

THE PRACTITIONER

No. 973

JULY 1949

Volume 163

EXAMINATION OF THE BLOOD

By JAMES INNES, M.D., F.R.C.P.Ed.

*Lecturer in Haematology, University of Edinburgh; Assistant Physician,
Royal Infirmary, Edinburgh.*

ALTHOUGH modern standard techniques in hæmatology are not difficult to perform, it is only those who work with them routinely who are likely to obtain results of sufficient and consistent accuracy. It is suggested that the general clinician should concentrate on accurate estimation of the hæmoglobin level and a careful study of a stained blood film. These two simple methods of examination can yield much information about many hæmatological conditions and indicate what more specialized laboratory data should be obtained.

HÆMOGLOBIN ESTIMATION

Many laboratories carrying out hæmoglobin estimation for routine and research purposes employ photo-electric apparatus for accuracy and speed in working. Among the more simple methods, those of Sahli and Haldane are in wide use and with care can provide reasonably reliable data. Using the Sahli type instrument, the blood hæmoglobin is converted to acid hæmatin by 0.1 N. hydrochloric acid and after a specified time the resulting brown colour is compared with a standard rod of glass. In the Haldane hæmoglobinometer the blood is diluted with water and saturated with coal gas, and the shade of pink carboxyhæmoglobin formed is compared with a standard tube. In both these methods the main source of error lies in the ability of the observer to match the blood sample with the standard colour and, as the latter tend to fade, it is advisable that the instruments should be checked periodically in a hæmatological laboratory. The Haldane technique is probably the most reliable method apart from photo-electric determinations, but the need for a supply of coal gas is an obvious objection. The Tallquist method, in which undiluted blood collected on a piece of absorbent paper is compared with a printed colour scale, is cheap and rapid but is grossly inaccurate and should not be used.

EXAMINATION OF A STAINED BLOOD FILM

A common mistake in the preparation of films is to make them too thick. Scrupulously clean glassware is essential, and the use of a suitable glass spreader may assist in the uniform spreading of a really thin film with the

THE PRACTITIONER

No. 973

JULY 1949

Volume 163

EXAMINATION OF THE BLOOD

By JAMES INNES, M.D., F.R.C.P.Ed.

*Lecturer in Haematology, University of Edinburgh; Assistant Physician,
Royal Infirmary, Edinburgh.*

ALTHOUGH modern standard techniques in haematology are not difficult to perform, it is only those who work with them routinely who are likely to obtain results of sufficient and consistent accuracy. It is suggested that the general clinician should concentrate on accurate estimation of the haemoglobin level and a careful study of a stained blood film. These two simple methods of examination can yield much information about many haematological conditions and indicate what more specialized laboratory data should be obtained.

HÆMOGLOBIN ESTIMATION

Many laboratories carrying out haemoglobin estimation for routine and research purposes employ photo-electric apparatus for accuracy and speed in working. Among the more simple methods, those of Sahli and Haldane are in wide use and with care can provide reasonably reliable data. Using the Sahli type instrument, the blood haemoglobin is converted to acid haematin by 0.1 N. hydrochloric acid and after a specified time the resulting brown colour is compared with a standard rod of glass. In the Haldane haemoglobinometer the blood is diluted with water and saturated with coal gas, and the shade of pink carboxyhaemoglobin formed is compared with a standard tube. In both these methods the main source of error lies in the ability of the observer to match the blood sample with the standard colour and, as the latter tend to fade, it is advisable that the instruments should be checked periodically in a haematological laboratory. The Haldane method is probably the most reliable method apart from photo-electric terminations, but the need for a supply of coal gas is an obvious objection. The Tallquist method, in which undiluted blood collected on a piece of absorbent paper is compared with a printed colour scale, is cheap and rapid but is grossly inaccurate and should not be used.

EXAMINATION OF A STAINED BLOOD FILM

A common mistake in the preparation of films is to make them too thick. Scrupulously clean glassware is essential, and the use of a suitable glass spreader may assist in the uniform spreading of a really thin film with the

edges well inside the width of the slide. Many workers prefer to make film preparations on cover-slips which form thinner smears with a more even distribution of leucocytes. After drying, the film is stained by one of the modifications of the Romanowsky method, Leishman's stain being the one most used in Britain. It is advisable to get to know the staining details of one particular brand of stain and its behaviour after storage, and in respect of the reaction of the water used for washing the preparation. A correctly stained film is pink to the naked eye, has pink erythrocytes, and the leucocytes have clearly differentiated nuclear staining and well-defined granules. Examination of the stained film should be made using the oil-immersion lens and noting the following points:—

Erythrocytes.—These are normally of fairly uniform size and shape, and show a suggestion of central pallor. In many anæmic states the red cells show variation in size, shape and degree of filling with hæmoglobin. In the iron deficiency type of anæmia, which is the most common type of anæmia in Britain, the cells tend to be small with a marked degree of central pallor. In contrast, anæmias of the pernicious type have large red cells, fully filled with hæmoglobin. Both varieties show anisocytosis and poikilocytosis. Very small, densely stained microspherocytes are present in some cases of hæmolytic anæmia. Nucleated red cells are not normally encountered in the peripheral blood. Their presence as normoblasts with pyknotic nuclei may indicate active blood regeneration, as after severe hæmorrhage or hæmolysis, or their premature extrusion from the marrow by some irritative or infiltrative process. Larger nucleated red cells may appear in untreated pernicious anæmia. Young red cells stain a purplish colour with Romanowsky stains and appear as reticulocytes if a drop of fresh blood is examined on a slide previously prepared with a 1 per cent. alcoholic solution of brilliant cresyl blue. In malaria infections the parasites may be found in the erythrocytes, and punctate basophilia may appear in cases of lead poisoning.

Leucocytes.—These should be scattered fairly evenly throughout the film, although the polymorphonuclear forms tend to collect along the edges. In making a differential leucocyte count, microscope fields should therefore be chosen from both the edges and centre parts of the film. It should first be decided whether the total white cell count is approximately normal or whether it is increased or diminished. With practice it is possible to recognize the scatter of leucocytes expected when the total count is within normal limits. Next, the individual cell types are noted in relation to the normal differential count. The figures for the latter are approximately: neutrophil polymorphonuclears 65 per cent., lymphocytes 30 per cent., monocytes 3 per cent., eosinophils 1.5 per cent., and basophils 0.5 per cent. In a differential count a minimum of 200 cells should be recorded. It should now be possible to decide whether a total leucocytosis results from a polymorphonuclear increase, as in pyogenic infections; a lymphocytosis, as in whooping-cough; a monocytosis, as in glandular fever; or an eosinophilia, as in certain parasitic infections. In leukæmia the total white cell count may be

greatly increased, particularly in the chronic myelogenous and lymphatic types, when a glance at the film may indicate the diagnosis with the finding of very large numbers of granular leucocytes or lymphocytes. In acute leukæmia the total count may also be raised considerably, with many immature cells present.

In leucopenia the low total count may be due to diminution of the neutrophil polymorphonuclears alone, as in enteric fever or agranulocytosis, or to depression of all leucocytes, as in some forms of marrow aplasia.

Next, the leucocytes are examined for signs of immaturity. With granular white cells, multilobulation of the nucleus is a sign of age, the youngest cells having the most simple nuclear shape. Young granulocytes with horse-shoe shaped nuclei may appear in the peripheral blood when severe infections such as lobar pneumonia cause a sudden polymorphonuclear leucocytosis, but myelocytes, more immature granular cells with rounded nuclei, are rarely seen in the normal blood. With lymphocytes and monocytes a large size of the cells and their nuclei is often an indication of immaturity. Cells showing nucleoli in their nuclei are never seen in normal peripheral blood and their presence in any number in a film is of the greatest significance. Nucleolated white cells are "blast" cells and occur in the peripheral blood in acute leukæmia.

Platelets.—Examination of the blood film is completed by studying the platelets. Normally these are found in occasional small groups, and when present in such numbers it is safe to assume that no gross thrombocytopenia exists. Inability to find platelets may result from their adherence to the spreader, and thrombocytopenia cannot be diagnosed on such evidence alone. Very numerous platelets may occur in the blood in polycythæmia vera, chronic myelogenous leukæmia, or after splenectomy.

DIAGNOSTIC USES

In general, a normal hæmoglobin level and blood film exclude the diagnosis of untreated anæmia and many other hæmatological disorders, and all cases in which these findings are abnormal require fuller laboratory examination. When the patient cannot attend a centre for this, the use of Wintrobe's oxalate mixture allows a sample of 3 ml. of venous blood to be sent for examination. On such correctly oxalated blood, counts can be made of red and white corpuscles and reticulocytes, and differential leucocyte counts, film examination and estimation of absolute indices and blood sedimentation rate carried out. As leucocytes degenerate after about six hours in oxalate, they should be studied as soon as possible and the laboratory should also receive a thin unstained film made on withdrawing the blood. Platelet counts are unsatisfactory on oxalated blood, with low results common. Plasma prothrombin time can be estimated on a Wintrobe sample for up to three hours. Wintrobe's oxalate mixture is prepared by dissolving 1.2 g. of ammonium oxalate and 0.8 g. of potassium oxalate in 100 ml. of neutral distilled water: 0.3 ml. of this solution is evaporated to dryness in a Wasser-

edges well inside the width of the slide. Many workers prefer to make film preparations on cover-slips which form thinner smears with a more even distribution of leucocytes. After drying, the film is stained by one of the modifications of the Romanowsky method, Leishman's stain being the one most used in Britain. It is advisable to get to know the staining details of one particular brand of stain and its behaviour after storage, and in respect of the reaction of the water used for washing the preparation. A correctly stained film is pink to the naked eye, has pink erythrocytes, and the leucocytes have clearly differentiated nuclear staining and well-defined granules. Examination of the stained film should be made using the oil-immersion lens and noting the following points:—

Erythrocytes.—These are normally of fairly uniform size and shape, and show a suggestion of central pallor. In many anæmic states the red cells show variation in size, shape and degree of filling with hæmoglobin. In the iron deficiency type of anæmia, which is the most common type of anæmia in Britain, the cells tend to be small with a marked degree of central pallor. In contrast, anæmias of the pernicious type have large red cells, fully filled with hæmoglobin. Both varieties show anisocytosis and poikilocytosis. Very small, densely stained microspherocytes are present in some cases of hæmolytic anæmia. Nucleated red cells are not normally encountered in the peripheral blood. Their presence as normoblasts with pyknotic nuclei may indicate active blood regeneration, as after severe hæmorrhage or hæmolysis, or their premature extrusion from the marrow by some irritative or infiltrative process. Larger nucleated red cells may appear in untreated pernicious anæmia. Young red cells stain a purplish colour with Romanowsky stains and appear as reticulocytes if a drop of fresh blood is examined on a slide previously prepared with a 1 per cent. alcoholic solution of brilliant cresyl blue. In malaria infections the parasites may be found in the erythrocytes, and punctate basophilia may appear in cases of lead poisoning.

Leucocytes.—These should be scattered fairly evenly throughout the film, although the polymorphonuclear forms tend to collect along the edges. In making a differential leucocyte count, microscope fields should therefore be chosen from both the edges and centre parts of the film. It should first be decided whether the total white cell count is approximately normal or whether it is increased or diminished. With practice it is possible to recognize the scatter of leucocytes expected when the total count is within normal limits. Next, the individual cell types are noted in relation to the normal differential count. The figures for the latter are approximately: neutrophil polymorphonuclears 65 per cent., lymphocytes 30 per cent., monocytes 3 per cent., eosinophils 1.5 per cent., and basophils 0.5 per cent. In a differential count a minimum of 200 cells should be recorded. It should now be possible to decide whether a total leucocytosis results from a polymorphonuclear increase, as in pyogenic infections; a lymphocytosis, as in whooping-cough; a monocytosis, as in glandular fever; or an eosinophilia, as in certain parasitic infections. In leukæmia the total white cell count may be

A full study of the white blood cells is essential if there is any suspicion of immature or abnormal forms present in the peripheral film, irrespective of the numbers in which they have been seen. The diagnosis of leukaemia may be very simple or extremely difficult on studying the peripheral blood, and repeated films may need to be examined, especially in cases with profound leucopenia. An important differential diagnosis is that of infectious mononucleosis from monocytic leukaemia. The characteristic cells of glandular fever are atypical lymphocytes, but it may need considerable experience to settle the diagnosis, especially when the Paul-Bunnell test is indecisive.

The hæmorrhagic diseases.—The patient is often seen because of bleeding after dental extraction or minor injuries, or because of a petechial eruption or persistent menorrhagia. A clear family history of a bleeding tendency is often not obtainable, although the patient may tell of some relative who also bleeds rather freely on occasion. Such cases should be examined for anaemia and the blood film searched to exclude leukaemia and thrombocytopenia. Absence of platelets from a single blood smear does not necessarily mean that thrombocytopenia exists, and platelet counts will be required to settle this point. Estimation of the bleeding time, which is the time required for bleeding to cease spontaneously from a small stab wound, will give information about the platelet function and capillary state. Blood coagulation is best studied by Lee and White's method, recording the clotting time of venous blood samples in test tubes. The capillary tube method is less accurate when the clotting is delayed. Clot retraction studies are useful in thrombocytopenia. When it is believed that delayed blood coagulation results from a low plasma prothrombin, determination of the prothrombin time by Quick's method should be performed. Repeated studies of plasma prothrombin are essential in cases receiving dicoumarin as anticoagulant therapy.

EXAMINATION OF THE BONE MARROW

Within the last fifteen years bone marrow biopsy has been established as a diagnostic procedure in blood disorders. Sternal puncture, first proposed by Arinkin in 1927, has come into wide use and is no more difficult or hazardous than lumbar puncture. Its limitations depend only upon the special skill necessary to make satisfactory marrow preparations for examination, and the expert knowledge required for interpretation of cytological findings.

The technique of *sternal puncture* is briefly as follows:—

Premedication of the patient is unnecessary, but in nervous subjects a sedative one hour beforehand is advisable. The skin over the sternum is carefully cleansed and, using a hypodermic needle, the skin, subcutaneous tissues and periosteum are infiltrated with 2 per cent. procaine over the midline of the bone opposite the second intercostal space. The anæsthetic must be injected beneath the periosteum and adequate time allowed for its full effect before inserting the sternal puncture needle, of which the Salah type is very satisfactory. The needle stopguard is set to a depth of about 1 cm. for an adult, and with the stylet in position the needle is held firmly at right angles to the bone and inserted into the outer table of the sternum, being pressed and rotated until a sensation of "give" is felt as the marrow cavity is entered. The stylet is removed and 1 to 2 ml. of marrow fluid are withdrawn into a tight-fitting 5 ml. syringe. A painful sucking sensation is experienced

mann tube scratched to indicate the 3 ml. level for the addition of venous blood. The tube must be well shaken immediately after adding the blood.

Anæmia.—A red blood cell count should be performed in all patients with a subnormal hæmoglobin level. From these two figures and the film appearances it can be settled whether the erythrocytes are small and hypochromic, as in iron deficiency anæmia, or large and fully filled with hæmoglobin, as in pernicious anæmia. A proportionate depression of the red cell count and hæmoglobin level occurs in aplastic anæmia. It is essential to establish the type of blood picture before starting treatment, especially with liver, for if pernicious anæmia is suspected the practitioner should be certain of the diagnosis before launching the patient on a lifetime of maintenance therapy. Many laboratories determine the packed red cell volume and calculate the mean cell volume and mean corpuscular hæmoglobin concentration in cases of macrocytic anæmia. Absolute indices are rarely needed in diagnosing straightforward cases of iron deficiency anæmia.

Examination of the white blood cells commonly shows a leucopenia with a relative lymphocytosis in pernicious anæmia. In marrow hypoplasia the leucocytes, especially the granulocytes, are usually much diminished in the peripheral blood and a platelet count may reveal an accompanying thrombocytopenia.

Regular blood examination is a necessary guide to the response to therapy in pernicious and iron deficiency anæmias. In the former, liver treatment promotes active erythropoietic stimulation with young red cells demonstrable in the peripheral blood from about the fourth to the tenth day. The percentage of reticulocytes should be estimated repeatedly during this period. Later, the red blood cell count and hæmoglobin level should be followed to see that normal figures are reached and maintained, indicating that liver therapy is adequate. Patients with marked iron deficiency anæmia receiving iron therapy should regain a normal hæmoglobin level at the rate of approximately one per cent. per day.

In cases in which hæmolytic anæmia is suspected, full blood examination is desirable. Frequent reticulocyte counts must be estimated, as the finding of active erythrocyte regeneration with a falling hæmoglobin level and red cell count constitutes strong evidence of hæmolysis when no blood loss is occurring. In hæmolytic anæmia the red corpuscles should be investigated in respect of their ability to withstand exposure to hypotonic saline. A fairly fresh specimen of blood, oxalated by Wintrobe's method, can be used for this fragility test.

Disorders affecting the leucocytes.—Total differential leucocyte counts are necessary when any deviation from the normal leucocyte picture is suspected. They are used routinely in hospital practice in the diagnosis and progress assessment of many infective conditions, and when treatment is being given with agents known to produce leucopenia as a toxic manifestation. Thiouracil, gold and the sulphonamides are drugs with which continued administration requires repeated checks on the leucocyte count.

BIOPSY

By CUTHBERT E. DUKES, O.B.E., M.D., M.Sc., D.P.H.

*Director of Research Laboratory, St. Mark's Hospital, London; Pathologist,
St. Peter's Hospital for Stone; Past President, Association of Clinical
Pathologists.*

THE value of biopsy in the diagnosis of tumours is well known. It is being resorted to more frequently for this purpose and also for the diagnosis of other diseases, and sometimes even for the control of treatment. For instance, a recent development is the use of biopsy for judging the progress of radiation and hormone therapy. Much of this is still in an experimental stage but the many well-established uses of biopsy justify consideration of this subject in a symposium on clinical pathology.

Biopsy consists in removing pieces of tissue from the living body for chemical or microscopic examination. If the lesion to be examined is on an exposed surface, a fragment may be removed by a scalpel or cutting forceps. For a biopsy of the skin all that is really necessary is a sharp knife and some local anæsthetic, so that a narrow strip of skin can be removed, cutting down deep enough to include the whole cutis and parts of the sub-cutis. A full description of the technique of skin biopsy is given by Freudenthal (1947).

The taking of satisfactory biopsies from internal organs such as the uterus, bronchus, bladder, or rectum, requires experience and the use of special instruments. In fact, in some cases the taking of a biopsy should be regarded as a minor surgical operation. It is not the purpose of this article to describe how such biopsies should be taken or even how the histology should be interpreted, but references will be given to articles and books in which these questions are fully considered by experts. Here, only the clinical indications and uses of biopsy will be discussed.

RISKS OF SURGICAL BIOPSY

Before proceeding further, a question which is always raised sooner or later must be answered, namely, is there any risk in biopsy? This question is of special importance in relation to biopsies of tumours because of the fear that the trauma of biopsy may result in more rapid spread of the disease. For instance, it is sometimes contended that biopsy may precipitate or provoke the change from a benign cutaneous mole to a malignant melanoma, with disastrous results to the patient. Freudenthal (1947) discusses this question but says that he has never seen any ill-effects in many soft moles excised or cauterized. However, he advises that great care should be taken

by the patient. The stylet is replaced before the needle is removed and pressure is applied over the puncture before affixing a dressing. A satisfactory technique for making examination preparations from the marrow fluid obtained is to pick out tiny flecks of marrow and spread them as smears on clean glass slides. The films are stained with a Romanowsky type stain. In addition, fixed preparations of marrow flecks can be made for histological sectioning.

In conditions such as marrow aplasia, in which sternal puncture may yield no marrow, or when it is desired to examine a wider distribution of bone marrow, puncture of the iliac crest or vertebral spinous processes may be performed. The iliac crest is often punctured in children in preference to the sternum. In rare cases of myelofibrosis the minor operation of sternal trephine may be necessary to provide a suitable biopsy section for diagnosis.

As the cellular elements of the blood are formed in the marrow, examination of the latter is especially helpful in investigating obscure hæmatological disorders. Marrow smears are of great value in diagnosing aleukæmic forms of leukaemia associated with leucopenia in the peripheral blood. In multiple myelomatosis, a characteristic marrow picture may be the one diagnostic feature early in the disease. In agranulocytosis, marrow examination often reveals whether the change results from an aplastic process or whether the granulocyte precursors are affected by a temporary maturation arrest, and treatment and prognosis will be based largely on these findings. Likewise, in cases with thrombocytopenia the outlook will to a certain extent depend upon whether megakaryocytes are present in sufficient numbers in the marrow. In kala-azar, malaria and trypanosomiasis, sternal puncture may show the causal parasites when they are not obvious in the peripheral blood, and the procedure is considered safer than spleen puncture. The characteristic foam cells of the lipoid storage diseases, such as Gaucher's disease and allied disorders, may be found in sternal marrow smears. Occasionally, the discovery of malignant epithelial cells in a marrow film may be the only direct evidence of carcinomatosis.

In most cases of anæmia the diagnosis can be made and the appropriate form of therapy instituted on the basis of the peripheral blood findings and clinical examination. Marrow examination only becomes necessary when the response to treatment is unsatisfactory or in rare cases when the nature of the anæmia is uncertain. In general, the iron deficiency anæmias and hæmolytic anæmias are associated with a normoblastic marrow picture. On the other hand, megaloblastic erythropoiesis is seen in the marrow in pernicious anæmia, some cases of sprue and tropical macrocytic anæmia, and in the megaloblastic anæmia of pregnancy. The latter rare condition can only be diagnosed by marrow examination. In true aplastic anæmia a hypoplastic marrow picture is present. Sternal puncture has proved of great value in academic research but is now recognized to have a wide practical application in clinical medicine.

References

- Lee, R. I., and White, P. D. (1913): *Amer. J. med. Sci.*, **145**, 495.
 Quick, A. J., Brown, M. S., and Bancroft, F. W. (1935): *Ibid.*, **190**, 501.
 Wintrobe, M. M. (1946): "Clinical Hæmatology", London.

it is carried out by an experienced hæmatologist and all goes well. The interpretation of the results of the bone marrow biopsy, however, is often far from easy and is best left to clinical pathologists who have made a special study of hæmatology.

ENDOMETRIAL BIOPSY

The microscopical examination of fragments of endometrium removed by curettage is of value in many different circumstances. It may provide evidence of hormone imbalance. If used for this purpose the time in the menstrual cycle at which the biopsy is taken becomes of importance because the examination must be made when the effect of the luteal hormone may be expected, namely, from two to five days before the onset of a menstrual period. For example, if the endometrium is found to be still in a non-secretory phase at a time when secretory activity should have started, this usually indicates an absence of ovulation. In other cases, endometrial biopsy may reveal atrophic or hypertrophic, or cystic non-secretory endometrium. These are important observations. In cases of abortion with retained products of conception the curettings may show chorionic villi and decidual cells mixed with blood clot. Moreover, the examination of curettings is a valuable aid to the diagnosis of malignant disease of the uterus. It may reveal adenocarcinoma of the fundus, squamous cell carcinoma of the cervix or a hydatidiform mole. A correct histological diagnosis of uterine curettings can only be given by clinical pathologists who have acquired sufficient experience in this type of work. Lloyd (1947) gives a good account of endometrial biopsy, well illustrated with pictures of normal and pathological findings.

BIOPSY IN RECTAL DISEASE

In rectal disease, biopsy is best carried out by the use of Brüning's forceps, by means of which fragments can be obtained from lesions at any height that can be reached by a sigmoidoscope. From a lesion in the ano-rectal region, biopsy material can be obtained through a proctoscope, using either Brüning's forceps or a smaller instrument of the nasal punch forceps type. The technique of rectal biopsy is well described by Gabriel (1948), who was one of the first to advocate the routine use of this method of examination.

It is now sixteen years since at St. Mark's Hospital the taking of a biopsy became part of the routine examination of a patient with suspected rectal cancer. Before this time it had been resorted to only in obscure cases, but after Gabriel's paper in 1931, entitled "Removal of Portions of Malignant Tumours of the Rectum for Confirmatory Sections", it was adopted as a regular routine procedure. Experience has shown that there is no danger of

to ensure that one is dealing with a mole without any signs suggestive of malignancy. If there is any doubt a complete excision with ample free margin all round is necessary.

It must, of course, be admitted that any form of injury or rough manipulation may accelerate the growth of a tumour, but experience has proved that if biopsy is carried out skilfully with the minimum of trauma it has no apparent effect on either a benign or malignant growth. But does it increase the liability to venous or lymphatic spread? To investigate this problem Paterson and Nuttall (1939) compared the course of two groups of patients with squamous cell carcinoma of the skin, in one of which biopsy was done and the other in which it was not. The incidence of metastases was then investigated and found to be the same in each group. As evidence of the harmless nature of biopsy a recent investigation in the Strangeways Laboratory at Cambridge may be quoted:—

Material for biopsy was taken frequently from a large group of patients treated by radiation for carcinoma of the uterine cervix. The five-year survival figures for these patients have been the same as for controls similarly treated by radiation but for whom no serial biopsies were taken. The taking of the biopsies had no adverse effect on the survival rate.

This question has also been discussed by Willis (1934), who says that experimental work has shown that incision into tumours or partial excision of tumours does not aggravate dissemination: hence, with certain reservations, excision of tumour fragments may be regarded as a harmless procedure.

ASPIRATION BIOPSY

In some cases material for examination may be obtained by puncturing with a needle and aspirating with a syringe. This is known as aspiration biopsy and would seem at first to have some advantages over surgical biopsy, using that term to describe removal of material by scalpel or other cutting instrument. It certainly has its uses and these are well described and illustrated by Hermitte and Ellis (1947). But it also has its limitations, because the recognition of tumour tissue in material provided by aspiration biopsy is more difficult than in fragments removed by surgical biopsy. Actually, aspiration biopsy is seldom of value in tumour diagnosis, but it is often useful in the search for parasites in spleen, liver, or lymphatic glands. Moreover, aspiration biopsy is the method of choice in obtaining material from the bone marrow. Sternal puncture is the method usually employed and this is a most valuable aid to the diagnosis of blood diseases. The Salah needle with an adjustable guard is the instrument most used in this country. A recent description of the technique of sternal puncture and a very complete interpretation of its findings is given by Dacie and White (1949), and in this symposium by Dr. Innes, on page 5. Sternal puncture is neither so painful nor so difficult as would be imagined; at any rate this is true when

TESTICULAR BIOPSY

Testicular biopsy may be used to obtain more information about cases of male infertility due to absence of spermatozoa in the semen. This may be due either to inactivity of the seminiferous epithelium of the testicle or to obstruction of ducts in the epididymis. These two conditions may be distinguished by testicular biopsy, a good description of the technique of which is given by Wiesner (1947).

BRONCHIAL BIOPSY

The interpretation of bronchial biopsies is one of the more difficult tasks in morbid histology, and very serious decisions may depend upon it. If the lesion is capable of being treated by surgery and the verdict of the biopsy is non-malignant the surgeon may decide to do a lobectomy, whereas if malignant, he may wish to perform a pneumonectomy. The special problems involved in bronchial biopsy are well discussed by Gloyne (1945), who has had special experience of this work.

BIOPSY IN LIVER DISEASES

In recent years liver biopsy has been used for the investigation of various forms of hepatitis, and much knowledge has been gained this way, although liver biopsy has not become in any sense a routine diagnostic procedure, because it is not without danger (Dible, McMichael and Sherlock, 1943). For the diagnosis of liver disease it is rarely resorted to in this country, but at the Memorial Hospital, New York, and some other American Hospitals, suspected tumours of the liver are only accepted for irradiation if a definite histological diagnosis has been made. Details are given by Binkley (1939).

LYMPH NODE BIOPSY

Surgical removal of a lymph node for microscopical examination is a valuable aid to diagnosis in many obscure cases of glandular enlargement, particularly in Hodgkin's disease, sarcoidosis, lymphoid follicular reticulosis, and in many other lymphadenopathies now classified as reticuloses. In other cases, microscopical examination of an excised gland may clinch a diagnosis of tuberculosis, or reveal unsuspected cancerous metastases. The technique of lymph node biopsy and the interpretation of its histology are well described by Robb-Smith (1947), who has made a special study of this subject.

SERIAL BIOPSY FOR CONTROL OF RADIATION AND
HORMONE THERAPY

At the Strangeways Laboratories at Cambridge a new method of histological analysis has been developed by Glucksman (1941) and Glucksman and Spears (1945). The method consists in taking biopsies before, during and

spreading the disease as there might be, for example, in making an incision into a cancer of the breast in order to obtain material for section, because in the case of rectal cancer the fragment is taken only from the surface of the tumour without injury to surrounding tissues. Biopsy is of special value when the diagnosis is obscure, but even when there appears to be no element of doubt, a confirmation of the clinical opinion is often welcome and there is ample time for a report on the sections before the operation of excision is undertaken. The records of St. Mark's Hospital prove that biopsy in rectal cancer is a trustworthy procedure.

Between the years 1930-45 inclusive, 2,118 biopsies were carried out preparatory to the operation of excision of the rectum for cancer, and in each case a comparison was made later between the original biopsy diagnosis and that of the tumour subsequently removed. In all but 17 cases there was agreement. In 15 of the 17 cases in which there was a discrepancy the biopsy report had been "villous papilloma", whereas subsequent examination of the operation specimen showed the growth to be a carcinoma. These were examples of carcinoma developing in a villous papilloma, and it just happened that the biopsy fragment had included only the non-malignant portion. In another case a carcinoma was wrongly reported in biopsy as a granuloma. In only one case was the biopsy diagnosis definitely misleading, this being a large endometrioma reported as an adenocarcinoma.

Biopsy has proved to be of special value in the diagnosis of lesions which clinically resembled malignant tumours but which actually were not so. These have included inflammatory lesions, cysts, unusual types of benign tumours, and lesions due to injection of hæmorrhoids with insoluble oils. In these and many other cases in which there was an element of uncertainty about the clinical diagnosis, the microscopical examination of a fragment removed by Brüning's forceps has provided information of the utmost value.

BIOPSY IN DISEASES OF THE BLADDER

The best method of obtaining a biopsy of a bladder neoplasm is by means of the Rongeur forceps applied through the operating cystoscope. Some experience is necessary to ensure that the fragments are taken from the most suitable place. A good account of the technique of such biopsy has been given by Aschner (1931) in a well illustrated paper. There is no doubt that reliable information about a tumour in the bladder can be obtained by biopsy in most cases. Aschner, in a large series of cases, considered that biopsy was worth while in 97 per cent. of cases. It is particularly useful for the correct diagnosis of lesions simulating neoplasms, such as tuberculous ulceration, leukoplakia, and granulomatous lesions. Even in cases of malignant disease in which the diagnosis is obvious by cystoscopic examination, biopsy may be worth while because it may provide additional valuable information, particularly with regard to the histological classification of the tumour, the grade of malignancy, the existence of metaplasia, and indications of the extent of spread.

TESTICULAR BIOPSY

Testicular biopsy may be used to obtain more information about cases of male infertility due to absence of spermatozoa in the semen. This may be due either to inactivity of the seminiferous epithelium of the testis or to obstruction of ducts in the epididymis. These two conditions may be distinguished by testicular biopsy, a good description of the technique of which is given by Wiesner (1947).

BRONCHIAL BIOPSY

The interpretation of bronchial biopsies is one of the more difficult tasks in morbid histology, and very serious decisions may depend upon it. If the lesion is capable of being treated by surgery and the verdict of the biopsy is non-malignant the surgeon may decide to do a lobectomy, whereas if malignant, he may wish to perform a pneumonectomy. The special problems involved in bronchial biopsy are well discussed by Gloyne (1945), who has had special experience of this work.

BIOPSY IN LIVER DISEASES

In recent years liver biopsy has been used for the investigation of various forms of hepatitis, and much knowledge has been gained this way, although liver biopsy has not become in any sense a routine diagnostic procedure, because it is not without danger (Dible, McMichael and Sherlock, 1943). For the diagnosis of liver disease it is rarely resorted to in this country, but at the Memorial Hospital, New York, and some other American Hospitals, suspected tumours of the liver are only accepted for irradiation if a definite histological diagnosis has been made. Details are given by Binkley (1939).

LYMPH NODE BIOPSY

Surgical removal of a lymph node for microscopical examination is a valuable aid to diagnosis in many obscure cases of glandular enlargement, particularly in Hodgkin's disease, sarcoidosis, lymphoid follicular reticulosis, and in many other lymphadenopathies now classified as reticuloses. In other cases, microscopical examination of an excised gland may clinch a diagnosis of tuberculosis, or reveal unsuspected cancerous metastases. The technique of lymph node biopsy and the interpretation of its histology are well described by Robb-Smith (1947), who has made a special study of this subject.

SERIAL BIOPSY FOR CONTROL OF RADIATION AND
HORMONE THERAPY

At the Strangeways Laboratories at Cambridge a new method of histological analysis has been developed by Glucksman (1941) and Glucksman and Spears (1945). The method consists in taking biopsies before, during and

after treatment and the carrying out of a differential cell count by classifying and counting tumour cells in selected comparable fields. This quantitative method of histological examination is now being used clinically for the selection of patients for radiotherapeutic or surgical treatment, and also to compare the efficiency of different radiological techniques in the treatment of carcinoma of the cervix. Several hospitals are collaborating in this research.

CONCLUSION

From what has been said it is obvious that biopsy is a reliable procedure and in many cases yields information which cannot be obtained in any other way. It is probable that its scope will be further extended in the future. Examples have been given of well-established applications of biopsy diagnosis and of others still in an experimental stage. As a last word it may well be pointed out that in some of the more difficult biopsies the best value from this method of examination can only be obtained if there is close cooperation between a clinician who knows when a biopsy would be useful, a surgeon who knows how to do it, and a pathologist who knows how to interpret the histology.

References

- Aschner, P. W. (1931): *Surg. Gynec. Obstet.*, **52**, 979.
 Binkley, J. S. (1939): *Amer. J. Cancer.*, **36**, 193.
 Dacie, J. V., and White, J. C. (1949): *J. clin. Pathol.*, **2**, 1.
 Dible, J. H., McMichael, J., and Sherlock, S. P. V. (1943): *Lancet*, **ii**, 402.
 Freudenthal, W. (1947): in "Recent Advances in Clinical Pathology", London, chap. 37.
 Gabriel, W. B. (1931): *Brit. med. J.*, **i**, 52.
 — (1948): "The Principles and Practice of Rectal Surgery", 4th edition, London, p. 353.
 Gloyne, S. R. (1945): *Proc. Ass. clin. Pathol.*, p. 31.
 Glucksman, A. (1941): *Brit. J. Radiol.*, **14**, 187.
 —, and Spears, F. G. (1945): *Ibid.*, **18**, 313.
 Hermitte, L. C. D., and Ellis, F. (1947): in "Recent Advances in Clinical Pathology", London, chap. 32.
 Lloyd, O. L. (1947): in "Recent Advances in Clinical Pathology", London, chap. 37.
 Paterson, R., and Nuttall, J. R. (1939): *Amer. J. Cancer*, **37**, 64.
 Robb-Smith, A. H. T. (1947): in "Recent Advances in Clinical Pathology", London, chap. 34.
 Wiesner, B. P. (1947): in "Recent Advances in Clinical Pathology", London, chap. 35.
 Willis, R. A. (1934): "The Spread of Tumours in the Human Body", London, chap. 13.

EXAMINATION OF THE STOOLS

By H. B. MAY, M.D., M.R.C.P.

Director, Clinical Laboratories, London Hospital.

No practitioner would omit to look at the stool of a patient with jaundice, but it is equally important to do so in the case of the pale patient who may not complain of any abnormality of his stools but who yet may be bleeding into his stomach or intestine. Unfortunately, the appearance of the *fæces* is often only characteristic in the most advanced stage of the disease, and this is especially the case in idiopathic steatorrhœa. Again, the stools in cases of bacillary dysentery, amœbic dysentery and ulcerative colitis may all look alike. It is fallacious to suppose that in bacillary dysentery there is pus and blood in the motion whereas in amœbiasis there is mucus and blood; this may be true in a few cases but it is an unreliable guide to diagnosis. Mucus which is clearly visible in *fæces* always indicates a pathological condition of the bowel, and the more intimately it is mixed with the *fæces* the higher up the intestinal tract is its source.

MICROSCOPICAL EXAMINATION OF FÆCES

Microscopical examination should never be omitted in the examination of any specimen of stool, but it is essential that the specimen should be fresh. In patients with suspected *amœbiasis* it is preferable to make arrangements with the laboratory for the patient to attend there and pass a stool rather than send the specimen to the pathologist. Daily specimens should be examined over a period of at least a week before a negative result can be established. To test for cure after emetine treatment the criteria of Hargreaves (1945) should be used, i.e., three daily stools in the second week after treatment and six daily stools after a further interval of one month.

The demonstration of adult *oxyuris* may be difficult. The patient will often declare that threadworms have been present in specimens of stool even when the laboratory report is negative. In such cases it is wise to encourage the patient to go to the laboratory and demonstrate to the pathologist the material which he thinks is a threadworm; this may be a vegetable fibre, but occasionally the patient is proved to be correct. For the demonstration of ova of *oxyuris* a cellophane-covered test tube pressed on the anal margin is preferable to a specimen of stool, but such material must be examined soon after it has been taken.

THE EXAMINATION OF STOOLS FOR FAT

The conception of the mechanism of absorption of fat from the intestine has been clarified by the work of Frazer and his colleagues. It was formerly postulated that fat must be completely hydrolysed before absorption can take place, but it has been shown that provided the unhydrolysed portion

is finely emulsified it can be absorbed, pass to the thoracic duct and thence to the fat depots. The neutral fat which appears in the stool does not therefore represent all the fat that has not been hydrolysed.

In the investigation of a specimen of stool for fat an adequate quantity is essential and most pathologists prefer about 4 to 8 ounces. A fluid stool is unsatisfactory, and the investigation should be postponed until the patient is passing a more solid stool, although it may still be formless. Is a single estimation of value? It must be admitted that in general a specimen taken at random with the patient on a varied diet is of little use and may actually be misleading. The percentage of fat present naturally varies with the amount of undigested residue, and the latter can vary considerably at different times of the day. Of course the typical stool of coeliac disease, which was so well described by Gee in 1888 as being loose, bulky, pale, frothy and stinking, is so characteristic that almost any such specimen will show a gross excess of fat, but the appearance alone is as diagnostic as exact chemical analysis. In cases of steatorrhœa of less severity, when fat analysis is essential for diagnosis, single specimens of stool may show results falling within what is commonly regarded as normal limits. It is to deal with such cases that the "fat balance" test was elaborated and this is essential for the accurate diagnosis of impaired fat absorption.

In the *fat balance test* the patient's absorption of fat is expressed as a percentage of the total fat ingested and he must therefore be on a standard fat intake; a reasonable diet would be one containing 50 g. of fat, 75 g. of protein, and 200 g. of carbohydrate. The duration of the test is commonly three days, and to mark the beginning of the test, carmine capsules are taken by mouth and collection of stools is begun when the first red colour appears. The end of the test is marked by the administration of charcoal in water, and collection of stools ceases when the black colour first appears. The whole of the stools passed in the three days is mixed, dried and analysed for fat; knowing the fat intake over the three days and the total fat excreted in the fæces the percentage absorption can be calculated. It has been shown by Cooke *et al.* (1946) that in normal people more than 91 per cent. of fat ingested is absorbed, whilst in cases of idiopathic steatorrhœa the average absorption is 73 per cent. with variation from 29 to 91 per cent. In order to simplify the test it is often adequate to put the patient on a standard diet for three preliminary days and then to give a saline enema after the evening meal; specimens of stool are collected for forty-eight hours, and at the end of this time another saline enema is given and the result added to the collected stools; the calculation is as before. From the pathologist's point of view the investigation is no more time-consuming than is the examination of a single specimen, and the result is far more valuable. If the duration of the test is shortened its accuracy is correspondingly reduced, and under such conditions most laboratories would accept an 85 per cent. or more absorption of fat as being normal.

The further examination of fat in fæces into split and unsplit fat is of little value. Lipase is secreted widely in the intestinal tract and is not confined to the secretion of the pancreas. In those cases of pancreatic disease in which the excess fat in the stools is unsplit the inference may be made that the secretion of lipase is minimal outside the pancreas and that disease of the pancreas can be inferred. The reverse, however, is by no means true, and there is no point in reporting the fat in stools as neutral fat, fatty acid, and fatty acid as soap. It is as well to mention here that the presence of fatty

acid crystals in stools is of no significance as indicating faulty fat metabolism.

The examination of the *fæces* for fat by the fat balance test should always be undertaken in cases of macrocytic anæmias with free hydrochloric acid in the gastric juice. A number of cases loosely described as achrestic anæmia or as refractory macrocytic anæmias are really cases of steatorrhœa without gross change in the stool.

THE EXAMINATION FOR OCCULT BLOOD

The benzidine test is a highly sensitive indicator of hæmoglobin in stools: it has been repeatedly shown that 3 to 5 ml. of blood given by mouth to a normal person on a hæmoglobin-free diet will give rise to a positive reaction. What value has the test in the diagnosis of gastric disease? Opinions are divided; there is no doubt that it is of little value in the diagnosis of peptic ulceration; it can be of use in the diagnosis of gastric carcinoma, but only if precautions are taken to see that the stool has been obtained under proper conditions. The patient must be on a hæmoglobin-free diet and the stool must be formed but not hard, so that there is no intestinal hurry or trauma by the passage of hard *fæces* along the bowel. With this *proviso* it has been said that three stools on successive days all negative for occult blood is good evidence against neoplasm. It may reasonably be held, however, that in a differential diagnosis of this importance a test which is open to such criticism is not worth doing, and that if the X-ray of the stomach is at all suspicious, laparotomy should be undertaken, whatever the result of the tests for occult blood.

It is interesting to note, as was shown by Schiff *et al.* (1942), that typical tarry stools result in normal people by the ingestion of 100 to 200 ml. of blood and that a positive occult blood test continues subsequently for five to fourteen days. In a normal person, stools become negative to the occult blood test after three days on a meat-free diet, and therapeutic doses of iron will not affect the result of the test.

THE EXAMINATION OF STOOLS FOR UROBILINOGEN

Fæcal urobilinogen is derived from hæmoglobin and the greater the breakdown of hæmoglobin the larger will be the excretion of urobilinogen; the test is therefore a delicate index of excessive red cell destruction (Maclagan, 1946). The excretion of urobilinogen can be shown to be increased before the serum bilirubin is raised. The amount excreted in twenty-four hours depends upon the total amount of hæmoglobin in the body, and Miller *et al.* (1942) suggested that the "hæmolytic index" should be used, i.e., the amount of urobilinogen excreted per 100 g. of circulating hæmoglobin rather than the total weight of urobilinogen excreted in twenty-four hours. Most workers, however, are satisfied with the latter figure. In normal people, from 80 to 240 mg. of urobilinogen are excreted per day, and in cases of hæmolytic anæmia the figure can rise to over 2000 mg. The stools

should be sent fresh to the laboratory and the average taken over a four-days' collection; delay in dispatching the stool may lead to considerable loss of urobilinogen. Faecal urobilinogen estimation is without doubt one of the most reliable methods of detecting a very mild hæmolytic anæmia.

THE BACTERIOLOGICAL EXAMINATION OF STOOLS

Considerable improvements have been made in the technique of the isolation of pathogenic organisms from stools and in their exact identification. These improvements have been reflected in the increased use being made by general practitioners of the facilities afforded by the Public Health Laboratory Service. For bacteriological examination only about half a teaspoonful of stool is necessary, and great care must be taken to see that it is sent to the laboratory in a container with a well-fitting lid. If a purge has been administered or if the patient has very loose stools the results obtained with a rectal swab are superior to those obtained from specimens of stool, but the rectal swab must be moistened with sterile water (not directly out of the tap, since tap water may have been chlorinated), and it must have been inserted 2 inches inside the anus. Fæces, and especially rectal swabs, must be delivered rapidly to the laboratory; specimens of fæces should be cooled to 10° C. if delay in delivery to the laboratory is likely to occur. When large numbers of stool specimens are to be examined bacteriologically a practitioner may find it convenient to use throat swabs dipped in a freshly passed specimen of stool.

In the investigation of cases of suspected typhoid or salmonella infection the stool is first inoculated into a fluid medium, e.g. tetrathionate or selenite broth, and after twenty-four hours is subcultured on to a further selective solid medium such as desoxycholate citrate agar. Suspicious colonies are then subcultured and their biochemical reactions determined. By the subsequent use of the appropriate absorbed sera the precise nature of the organism can be ascertained.

It will be seen that a result may not be available for three days and in certain cases for an even longer time, but the investigation is considerably more reliable than was the case ten years ago. Duration of carriage of pathogenic organisms and their excretion in the fæces can be very variable: the larger the number of stools that are examined the longer will be found to be the time during which the patient harbours the organism. As an arbitrary rule it is usual to obtain three negative stools at not less than two-day intervals and after a saline purge before the patient is declared free of infection. In the investigation of cases of diarrhœa and in the detection of carriers, as in all other laboratory tests, the best results are obtained when the closest cooperation is established between physician and clinical pathologist.

References

- Cooke, W. T., *et al.* (1946): *Quart. J. Med.*, 15, 141.
Hargreaves, W. H. (1945): *Lancet*, ii, 68.
MacLagan, N. F. (1946): *Brit. J. exp. Path.*, 27, 190.
Miller, E. B., Singer, K., Dameshek, W. (1942): *Arch. intern. Med.*, 70, 722.
Schiff, L., *et al.* (1942): *Amer. J. med. Sci.*, 203, 409.

THROAT SWABS

By R. D. STUART, M.D., D.Sc., D.P.H.

Bacteriologist, Royal Infirmary Hospital Group, Glasgow.

A SWAB should be taken from the throat whenever the identification of the throat bacteria is likely to assist or confirm diagnosis. To obtain the best value from the examination three things are necessary:—

- (1) Correct manipulation of the swab.
- (2) Direction of the laboratory investigations into the most appropriate channels.
- (3) Intelligent interpretation of the report.

METHOD OF USING THROAT SWABS

First, see that the swab can be withdrawn readily from its tube. The cork to which it is usually attached may stick to the glass during sterilization and subsequently break or refuse to be dislodged just at the moment the one fleeting glimpse of a reluctant pharynx is obtained. Then examine the throat if possible without using a tongue depressor, which always stimulates resistance, at least in a child. When the nature of the lesion or area to be examined has been determined the operator must rub the swab firmly over this area and return it to its tube without touching any other surface. Assistance in the case of a child is almost essential.

The left hand of the parent or attendant should hold the child's wrists crossed over the chest and the right arm should encircle the patient's forehead. The practitioner should then insinuate the spatula held in his left hand inside the left cheek until it reaches the posterior alveolar margin, when the patient's mouth will usually open. With a quick movement the posterior third of the tongue is then pressed down firmly and the swab, ready in the other hand, is swept quickly but very firmly over the affected area. It must be emphasized that the whole operation at this stage should be completed as quickly as possible, almost coincidental with pressing down the tongue; the swab should be out of the mouth and back in its tube almost before the patient has had time to realize what has happened.

Ordinary faucial specimens are useless for certain investigations, such as for meningococci or whooping-cough bacilli. For these, swabs must be taken from the postnasal space and posterior pharyngeal wall. Special pernasal swabs are best for this type of examination, and indeed people who use them are enthusiastic on their value for most types of pharyngeal culture. In an emergency, an alternative can be improvised by bending to 45° the terminal inch of an ordinary throat swab and insinuating it behind the soft palate. Afterwards the swab can be straightened out and returned to its tube.

The ordinary precaution against the use of gargles or disinfectants, to which nowadays must be added penicillin given locally or generally, must of course be observed. It is usually recommended that no antibacterial substance should have been applied locally for at least two hours before taking a swab.

LABORATORY INVESTIGATION

The sooner a specimen is received in the laboratory after being taken the better, but diphtheria bacilli or hæmolytic streptococci, if present in considerable numbers, will usually survive for twenty-four hours in a specimen sent by post. Yet I would suggest that in any instance when the laboratory report on a specimen seems insufficient, then a second specimen should be brought directly to the laboratory.

Theoretically, the laboratory investigation should vary according to the clinical information received, but laboratories receiving large numbers of specimens are forced almost inevitably to follow certain routine procedures. If a practitioner thinks that the routine throat swab investigation of his local laboratory is insufficient for a particular specimen he should write "Special" across the form, or preferably tell the laboratory about it. This does not mean that the clinical information requested should not be supplied (it is often essential to the laboratory workers in their interpretation of findings), but unless there is some special indication the initial culture will proceed along certain routine lines. Usually a throat swab is investigated for diphtheria bacilli by culture on a serum medium (Loeffler's) and also on a blood agar tellurite medium. Culture on ordinary blood agar for hæmolytic streptococci is not necessarily a routine. Investigation for other bacteria, such as meningococci or pertussis organisms, requires special media and special methods. The presence of Vincent's organisms and other spirochætes cannot be determined successfully from a swab. A smear on a glass slide should be prepared directly from a lesion and submitted to the laboratory.

After eighteen to twenty-four hours' incubation of a Loeffler culture, microscopical examination, if supported by clinical findings, will often permit the report "diphtheria bacilli present". If such organisms are atypical, however, most laboratory workers prefer to wait another twenty-four hours for the results of the tellurite agar culture before committing themselves. A report on the presence of hæmolytic streptococci may often be obtained in twenty-four hours, but other bacteria may need longer; meningococci will take about four days, which is also about the minimum time for the isolation of *H. pertussis*.

It must be emphasized that from the laboratory worker's viewpoint these reports are generally tentative. In many instances he backs his experience against his knowledge that the investigation is incomplete, and he

assumes that practitioners realize this when they insist on a quick report to assist diagnosis.

INTERPRETATION OF THE REPORT

The last sentence of the preceding paragraph should indicate the attitude desirable in interpreting the average throat swab report, and consequently should suggest, if the report does not support the clinical findings or assist in the diagnosis, that the laboratory should be so informed. At this stage the more personal the association between laboratory and clinical worker the better the ultimate result. Most laboratory workers resent any "penny in the slot" implication and appreciate being considered part of a medical team.

Laboratory terminology sometimes causes perplexity to the clinician: β -hæmolytic streptococci are probably pathogens, but α -hæmolytic streptococci are ordinary viridans streptococci almost invariably present in the normal throat. Diphtheroid bacilli mean organisms belonging to the same generic group as the diphtheria bacillus. Most of these are non-pathogenic, but the term covers doubtful or atypical diphtheria bacilli which require further investigation before report. In such cases the examining laboratory generally indicates that a further report will be sent.

In investigating possible carriers and contacts simple culture is rarely sufficient. Some form of grouping or typing is usually necessary. Practically all strains of hæmolytic streptococci causing human disease belong to group A; within this group are many serological types which indicate final identification. The so-called typing of diphtheria bacilli into *gravis*, *intermedius* and *mitis* is not serological and is much less definite in identifying individual strains. Furthermore, this typing has little meaning in assessing the clinical severity of any single case; only in broad epidemiological surveys does the association of the first two with more serious disease become manifest.

An elementary but often forgotten point is that the laboratory report indicates merely the organisms on the swab. Most laboratory workers can recall cases of obvious diphtheria in which the swabs failed to reveal diphtheria bacilli. The infecting organisms were present only in the deeper areas of the mucous membrane and the swab removed other organisms multiplying more superficially. If a case looks like diphtheria, serum should be given without waiting for bacteriological confirmation. In every case the responsibility for identifying a disease process depends upon the clinical worker who is observing its appearance and the reaction of his patient to it, and the laboratory report should be regarded as a useful and often essential brick to build into the edifice of clinical diagnosis.

THE BACTERIOLOGICAL INVESTIGATION OF PULMONARY TUBERCULOSIS

FROM THE ASPECT OF CLINICAL PATHOLOGY

BY D. BARRON CRUICKSHANK, L.R.C.P., L.R.C.S.Ed., D.P.H., L.D.S.

*Clinical Pathologist, Sims Woodhead Memorial Laboratory,
Papworth Sanatorium, Cambs.*

SPUTUM EXAMINATION

THE sputum specimen should be representative and a "twenty-four-hour specimen" has many advantages: for example, it indicates the general characteristics and volume of the sputum; it tends to reduce the risk of "saliva specimens", so frequent with a single spit; it gives greater opportunity for "selecting" suitable proportions for examination, and often stimulates the production of sputum when such is scanty.

Preliminary examination by direct microscopy, using the Ziehl-Neelsen stain, is still an accepted procedure and serves as a standard against which all new methods are assessed. Although improved methods are now available and are gradually replacing the Ziehl-Neelsen technique they still lack the "psychological" security of the historically established and more fully tested Ziehl-Neelsen result. When typical acid-fast forms are demonstrated in the sputum they may be accepted as *M. tuberculosis*. Acid-fast saprophytes are occasionally associated with gangrenous conditions of the lung; when any doubt exists, confirmatory cultures should be made.

Although methods of *concentrating the sputum* can enhance the sensitivity of direct microscopy by factors varying from ten to fifty times they are not now generally used, except for "confirming" specimens which on preliminary examination were found to contain only a few scattered bacilli. They are now being replaced by "large field" methods; of these *fluorescence microscopy* is the best known. Here, although the effective field is ten, twenty or more times greater than that of the oil immersion field, the contrast between the bacilli (which are rendered self-luminous by staining with fluorescent dyes and illuminating with near ultra-violet light) and the unstained background is so great that the bacilli can be detected with low-power dry objectives. Optical definition is excellent and is enhanced by the phenomenon of irradiation which gives rise to an apparent increase in size of the bacilli. The advantages are a definite increase in the number of positives, approximately 17 per cent. additional to those found positive by the Ziehl-Neelsen technique in an average sanatorium population. Other "large field" methods which require less specialized equipment are also

available; the best known being that which employs a green filter (Wratten H45) in the condenser, so rendering the Ziehl-Neelsen-stained bacilli jet-black by complementary colour illumination; equivalence with fluorescence microscopy is claimed. A still simpler system is the use of picric acid counter-stain which increases contrast, but proves unfortunately very fatiguing to the eye. One great advantage of "large field" methods is the ability to "rediscover" rare bacilli noted at the initial examination of the film.

Culture.—At their best, all direct microscopic methods are crude and inadequate for efficient sputum examination; this always demands the use of some culture procedure. The sputum for culture must first receive preliminary treatment to eliminate secondary organisms. Contact with alkalis, although assisting homogenization, is rapidly deleterious and requires accurate timing to prevent destruction of tubercle bacilli. For this reason the use of 5 per cent. oxalic acid, which has a much greater safety time factor, is preferable. Organic acids are safer than inorganic acids (such as sulphuric) and yield a higher proportion of positive results.

The particular *medium* used is a matter of individual preference, but Lowenstein-Jensen or Petragani are quite reliable. Dubos medium is not suitable for primary isolation. Cultures should be made in duplicate; the use of a large number of tubes is unnecessary; two tubes net 99 per cent. and three tubes 99.9 per cent. of the theoretical positives isolatable on the particular media used. Multiple seeding is only recommended when a variety of media is employed. If screw cap tubes are used, these should be loosened at weekly intervals to admit oxygen, absence of which markedly retards growth.

Cultures are incubated at 37° C. for three weeks, by which time 85 per cent. of positives are revealed. If negative at this time run a loop over the surface and prepare a smear for direct microscopy; about 2.8 per cent. additional "micro-positives" are revealed at three weeks by this procedure. Replace the negatives for a further three weeks and re-examine, by which time 98 per cent. of the positives show up. Further incubation up to fifteen weeks gives only a 2 per cent. increased return and merely blocks valuable incubator space.

Animal inoculation tests, once regarded as greatly superior to cultures, are not now commonly used, as modern media for tubercle culture have a roughly equivalent sensitivity. When cultures and animal inoculations are employed concurrently there is a 10 per cent. increase in positives, but the extra positives are equally distributed between culture and animal results; thus culture is superior for a small proportion of strains and animal inoculation superior for another small proportion of strains. Taken by and large, culture is more sensitive for the isolation of human strains (91 per cent. culture; 84 per cent. animals) and animals more sensitive for the isolation of bovine strains (89 per cent. animal; 80 per cent. culture). The culture result is more rapid than the animal result.

When still greater speed is required *slide culture* methods can be employed. These will give a result in three to seven days. No slide culture method is yet entirely satisfactory; placed in fluid media they are liable to contamination or to diffuse and dangerous overgrowth of tubercle bacilli; when

THE BACTERIOLOGICAL INVESTIGATION OF PULMONARY TUBERCULOSIS

FROM THE ASPECT OF CLINICAL PATHOLOGY

By D. BARRON CRUICKSHANK, L.R.C.P., L.R.C.S.Ed., D.P.H., L.D.S.

*Clinical Pathologist, Sims Woodhead Memorial Laboratory,
Papworth Sanatorium, Cambs.*

SPUTUM EXAMINATION

THE sputum specimen should be representative and a "twenty-four-hour specimen" has many advantages: for example, it indicates the general characteristics and volume of the sputum; it tends to reduce the risk of "saliva specimens", so frequent with a single spit; it gives greater opportunity for "selecting" suitable proportions for examination, and often stimulates the production of sputum when such is scanty.

Preliminary examination by direct microscopy, using the Ziehl-Neelsen stain, is still an accepted procedure and serves as a standard against which all new methods are assessed. Although improved methods are now available and are gradually replacing the Ziehl-Neelsen technique they still lack the "psychological" security of the historically established and more fully tested Ziehl-Neelsen result. When typical acid-fast forms are demonstrated in the sputum they may be accepted as *M. tuberculosis*. Acid-fast saprophytes are occasionally associated with gangrenous conditions of the lung; when any doubt exists, confirmatory cultures should be made.

Although methods of *concentrating the sputum* can enhance the sensitivity of direct microscopy by factors varying from ten to fifty times they are not now generally used, except for "confirming" specimens which on preliminary examination were found to contain only a few scattered bacilli. They are now being replaced by "large field" methods; of these *fluorescence microscopy* is the best known. Here, although the effective field is ten, twenty or more times greater than that of the oil immersion field, the contrast between the bacilli (which are rendered self-luminous by staining with fluorescent dyes and illuminating with near ultra-violet light) and the unstained background is so great that the bacilli can be detected with low-power dry objectives. Optical definition is excellent and is enhanced by the phenomenon of irradiation which gives rise to an apparent increase in size of the bacilli. The advantages are a definite increase in the number of positives, approximately 17 per cent. additional to those found positive by the Ziehl-Neelsen technique in an average sanatorium population. Other "large field" methods which require less specialized equipment are also

Another important point is the *number of consecutive negative reports* which are required before sputum can confidently be regarded as negative by the test used. Expectoration of infective sputum is erratic and a series of negatives is necessary to offset this contingency and also the unavoidable inequalities of sampling. The definition of the "number" of results must always remain arbitrary for, to take an extreme case, a persistently negative sputum may become positive in the course of some intercurrent infection such as bronchitis or influenza. The use of three negative "direct smear" results, as recommended by the Ministry of Health, corresponds to a "limit" of approximately 4000 bacilli per ml., still some four hundred times less sensitive than the culture test.

A *re-definition of the criteria* of sputum conversion is one of the most pressing current needs. A reasonable working criterion of conversion is three successive negative culture results, the cultures being made at monthly intervals. This is, of course, a relatively stringent test, but it has been shown to have definite clinical meaning, for the relapse rate of cases discharged from sanatoria as negative by such cultural criteria is lower than that of discharged cases classified as positive by the same criteria within the last six months before discharge.

PLEURAL FLUIDS AND TUBERCULOUS COMPLICATIONS

Investigation of both *primary and secondary pleural effusions* and also of post-artificial pneumothorax, and less commonly of post-pneumoperitoneum effusions, is often needed in connexion with pulmonary cases. Here, the "Z.N. F.M. culture" sequence is used as with sputum, but it is usual to determine, in addition, the type and number of cells present and the percentage of protein. Hæmorrhagic pleural effusions may portend malignancy and require more detailed cytological study; here, estimation of the "age" of the blood by bilirubin estimations may assist in arriving at a diagnosis. When any of the above fluids become secondarily infected, full bacteriological investigation is required.

Other associated tuberculous conditions and complications include *tuberculous abscesses and glands*. Although pus from the latter may show bacilli on smear, these bacilli often fail to grow on culture. This phenomenon is also seen in pulmonary lesions when positive sputum from some patients in certain phases of the disease may contain bacilli remarkably sensitive to oxalic or alkaline treatment, so much so that they completely fail to grow when cultured. Hence, paradoxically enough, the Z.N. and F.M. are on occasion more sensitive than culture.

The bacteriological diagnosis of *intestinal tuberculosis* is almost impossible; these cases often arise in patients with heavy positive sputum and the source of faecal tubercle bacilli is very problematical; the presence of pus and blood may help. In suspected *renal tuberculosis*, cultures are prepared

placed on solid media a certain proportion of positives fail to grow. Such methods, although potentially valuable, are still in the experimental stage.

CASES WITH NO SPUTUM

When the patient is unable to raise sputum, specimens for examination can be obtained by various methods.

Gastric lavage recovers ingested sputum. Here, direct microscopy loses some of its specificity, as acid-fast organisms may derive from butter, milk, cheese, and the like. Culture is therefore desirable, at least in the case of weakly positive smears. Hydrochloric acid is inimical to tubercle bacilli and the specimen should be neutralized to bromothymol blue immediately after collection. Subsequent treatment of the neutralized lavage with oxalic acid gives excellent recoveries. Curiously enough the buffer content of Lowenstein-Jensen medium will effectively neutralize oxalic acid but has no effect on hydrochloric acid.

The use of *laryngeal swabs* is gaining popularity. These collect organisms in the tracheal droplet spray; hence they contain only relatively small numbers and the use of culture is imperative. It is essential to prevent inspissation of the droplets, and the swabs should be moistened before use and cultures made immediately after swabbing. Postal transit definitely diminishes positive returns.

Pulmonary lavage is claimed to give improved sampling conditions. Here, sterile saline is instilled down the trachea and the expectorated fluid lavages an extensive area of the bronchial mucosa and produces what is in effect the equivalent of sputum. Where a sanatorium is attached to a surgical unit mucous may be aspirated from bronchi with the sucker at bronchoscopy. With both the latter methods films are often found positive on direct microscopical examination.

ASSESSING THE RESULTS OF TREATMENT

Quite apart from diagnosis, sputum tests are most valuable in assessing the results of collapse therapy and other treatment. The essence of such examinations rests largely on serial quantitative estimates of bacterial concentrations. The original *criterion of sputum conversion* was a "negative direct smear" as determined by the standard Ziehl-Neelsen technique, but this is a crude estimate and sputa containing 20,000 tubercle bacilli per ml. may readily be missed. The use of fluorescence microscopy is a considerable improvement but still misses two-thirds of the (Ziehl-Neelsen negative) specimens which are subsequently found to be positive on culture. Culture, on the other hand, is a vastly more sensitive test, as the presence of a single colony, corresponding to approximately 10 bacilli per ml., indicates a definite positive result.

GLYCOSURIA

By ALEXANDER LYALL, M.D., F.R.C.P.

*Lecturer in Clinical Chemistry, University of Aberdeen; Specialist Physician,
Aberdeen Royal Infirmary.*

THE discovery of a reducing substance in the urine, whatever the nature of the case, puts a new aspect on the examination and care of the patient concerned. Two main questions immediately arise. Is the reducing substance glucose, and if so does it mean that the patient is suffering from diabetes mellitus? These questions must be answered at the earliest possible moment. The answer to the first question presupposes the knowledge that other reducing substances may be found in the urine from time to time. These comprise certain drugs, including rhubarb, senna, drugs of the antipyrine group, drugs excreted in combination with glycuronic acid, e.g. chloral, chloroform, and occasionally salicylates and iodides. If the presence of any drug is suspected in the urine it may be tested for, but the easiest method is to get a further sample of urine the next day when the urine is free of such complications.

SUGARS IN THE URINE

Sugars other than glucose may occur in the urine but practically the only sugar of consequence in this respect is lactose. This occurs only during *pregnancy*, usually not before the 7th month, and in *lactation*. It can be recognized as being non-fermentable by yeast. Glucose is, however, commonly present in the urine during pregnancy and often in the earlier months. If a reducing substance is found in the urine in a pregnant woman it is wise to have the fasting blood sugar determined. If this is normal, the condition can be watched and if necessary a full sugar tolerance test carried out later. Temporary renal glycosuria of pregnancy is a common condition but it must be kept in mind that diabetes may have its onset during pregnancy or even during lactation.

The other reducing sugars which may occur in the urine are *lævulose* (fructose), only rarely, as a metabolic abnormality, pentose or arabinose, and galactose. *Lævulose* and galactose may commonly be found in the urine of patients while under observation in hospital, since these sugars are sometimes given by mouth in tests for hepatic function. Their renal threshold is low and they invariably appear in the urine if taken by the mouth. On occasion, reducing sugars may be found in the urine as artefacts: when abnormal patients, usually with some medical training, add these substances to samples of urine for their own obscure reasons. These unusual sugars occur so rarely that in most clinics search for their recognition is instituted only when a bizarre type of glycosuria occurs which is not easily explained by the usual methods. In the great majority of cases a definite

from a "morning specimen", this having been proved usually to contain the greatest number of excreted bacilli. Animal inoculation and other tests may be needed to exclude *B. smegmatis*, but a positive direct smear from a "catheter specimen" may be accepted as a fairly specific result. Pus cells or albumin are usually present and hæmaturia may herald extension of the disease.

Tuberculous meningitis may supervene and require differentiation from an idiopathic condition. Bacilli are rarely found in the direct smear of the cerebrospinal fluid and culture growth is usually sparse; a raised cell count and a raised total protein are the earliest and most sensitive progenitors of a true tuberculous condition. Variations in chloride levels are of little guidance in the incipient stages. It is important to remember that 50 per cent. of the *otorrhœal discharges* in patients with positive sputum grow tubercle bacilli, although the incidence of tuberculous disease of the middle ear is of a much lower order.

SPECIAL BACTERIOLOGY

When *streptomycin* is used it is necessary to determine the "sensitivity" of the particular tubercle bacillus before treatment, and its acquisition of "resistance" to streptomycin during treatment. Both these procedures require cultural isolation of the tubercle bacilli from the sputum as a preliminary to their transference to a series of special media containing dilutions of streptomycin. In the case of both streptomycin and para-amino-salicylate treatments it may be necessary to determine the concentrations of these substances in the blood stream in order to adjust dosage.

Of almost equal moment is the general bacteriology of *secondarily infected empyemas* or other fluids. The full bacterial flora must be defined and, in the case of a mixed infection, the individual penicillin sensitivity assessed. If insensitive to penicillin, then sensitivity to various sulphonamides is checked (individual strains show a remarkable variation in this regard). If insensitive to all these, chemical antiseptics of the azochloramide or phenoxetol groups can be used. The advent of penicillin-resistant strains has considerably increased the need for these supplementary investigations.

It is occasionally necessary to *type bacilli as human or bovine*. Cultures on egg media, with and without glycerin, are then used, but animal inoculation of the resulting growth remains the final court of appeal. The rabbit, which is insensitive to human strains in appropriate inocula, rapidly succumbs to a similar dose of bovine culture suspension. The frequency of bovine pulmonary tuberculosis varies throughout the country from 7 per cent. in Scotland to 0.5 per cent. in the South of England; hence the demand for typing will vary with the locality. Mixed human and bovine infections are occasionally found, and the possibility of avian infection should be borne in mind.

GLYCOSURIA IN VARIOUS CONDITIONS

Glycosuria is found in association with a large number of conditions in routine practice or in hospital patients. No classification could be exhaustive, but glycosuria is a universal or usual finding in the following states besides diabetes mellitus:—

Hæmochromatosis or diabetes bronzé.

Hepatic diabetes of the obese in later decades.

Renal glycosuria.

Renal glycosuria of pregnancy.

So-called alimentary glycosuria.

So-called psychical glycosuria.

Certain surgical conditions, including gross sepsis, e.g. cellulitis, carbuncles and septic gangrene; severe traumatic injuries; acute pancreatitis; head injuries, and cerebral hæmorrhage.

After anæsthetics, especially chloroform and ether.

After administration of adrenaline.

In coal gas asphyxiation.

After administration of intravenous glucose saline.

Thyrotoxicosis, frequently.

Hyperpituitarism and fully developed acromegaly.

Cushing's syndrome and suprarenal tumour.

In the presence of clinical signs of obesity, pigmentation, acromegaly or Cushing's syndrome, glycosuria usually means associated diabetes. In the presence of severe sepsis, cellulitis, carbuncle, and septic gangrene, glycosuria also usually means associated diabetes, but in a proportion of these cases, even though hyperglycæmia be present, this may be transitory and disappear or be much ameliorated on suitable treatment, drainage and healing of the septic foci. In severe injuries, or some head injuries, temporary hyperglycæmia is present but is seldom followed on recovery by permanent diabetes. Nevertheless, permanent diabetes may be a sequel to a head injury such as a fall from a motor bicycle. After the administration of anæsthetics, adrenaline, glucose-saline, and coal gas, glycosuria is usually transitory. It is not uncommon to find temporary hyperglycæmia in young adults after operation for a gangrenous appendix. When obvious exophthalmic goitre is present, glycosuria usually means a temporary elevation of the blood sugar due to thyroxin stimulation, although occasionally true diabetes and thyrotoxicosis coexist. The more usual type of glycosuria is controlled after treatment with thiouracil.

In a recent instance in a male patient aged forty-four years referred for glycosuria, there were signs of exophthalmic goitre with tachycardia, loss of weight, sweating, enlargement of the thyroid gland, and basal metabolic rate plus 38 per cent. A glucose tolerance test gave the following figures for the blood sugar: 100, 156, 206, 181, 117 mg. per cent. After treatment with thiouracil the sugar tolerance test showed: 100, 140, 133, 109, 100 mg. per cent., and there was no glycosuria.

BLOOD SUGAR ESTIMATIONS

In all cases of glycosuria, *estimation of the blood sugar* is essential in making a definite diagnosis. For this purpose capillary blood may be taken by finger

reducing substance found with Fehling's test or Benedict's test is glucose. Exton (1936) found that in 97 per cent. of samples the sugar was glucose if the concentration was over 1 per cent.

IS DIABETES PRESENT?

Let us suppose that the reducing substance is glucose and that it is in fact glycosuria which is found. The second question must now be answered. Is the patient diabetic or not? Certain broad principles may help in a decision. If the amount of sugar is large the patient probably has diabetes. If symptoms or signs suggestive of diabetes, e.g. loss of weight, thirst, polyuria, nocturia, pruritus, are present, the diagnosis of diabetes is almost certain. If Rothera's test for acetone is positive, diabetes of moderate severity can be diagnosed with practical certainty.

The only exception to this rule is when a patient has had a starvation ketosis for some other reason, e.g., acute abdomen or hyperemesis gravidarum, and has already been treated with glucose. Temporarily the urine contains both glucose and acetone. If Gerhard's ferric chloride test for diacetic acid is positive there is severe diabetes in the stage approaching diabetic coma. The only precaution necessary here is to exclude the presence of previous treatment with aspirin or its compounds or with salicylates, which simulate this test.

The *specific gravity of the urine* may help. If the amount of sugar is large the specific gravity is usually about 1030 and may be up to 1044. This never occurs except in diabetes. But with copious polyuria and when the normal constituents of the urine are in great dilution, the specific gravity of the sample may not be higher than 1016 or 1018. So that a sample of urine within the normal range of specific gravity may still be diabetic.

Milder degrees of diabetes may show only slight glycosuria or even transitory glycosuria and here the diagnosis may remain in doubt, since no symptoms or signs may be elicited. Generally speaking, the chance finding of glycosuria in a young adult when no symptoms of diabetes are present or suspected, is likely in nine cases out of ten to be due to one of the types of simple glycosuria. Thus, in a series of investigations on 381 young adults showing glycosuria which was discovered accidentally on medical examination for the Services, 41 were found to be diabetic, 112 to have high normal curves, and 234 to be examples of renal glycosuria (Lyll, 1946).

When symptoms have aroused suspicion of the presence of diabetes, and glycosuria is found the chance is reversed. Glycosuria in both sexes over forty-five years of age is nearly always diabetic. In an individual who has previously passed medical examinations for the Services, a life insurance, or appointments, and when a new finding of glycosuria occurs, it probably means diabetes. When an individual has a previous record of glycosuria on several occasions over a few years, the glycosuria is almost certainly of a harmless type, especially if no dietetic or other treatment has been instituted.

ILLUSTRATIVE BLOOD SUGAR CURVES

Urine fasting			Blood sugar					Urine after test			Diagnosis and remarks
G. per cent.			Mg. per cent.					G. per cent.			
			Time in minutes								
			Fast- ing	30	60	90	120				
	Sugar	Albu- min	85	150	130	110	90	85	1.0	o	No symptoms. Renal glycosuria.
	0	o	85	120	110	90	65	2.0	trace	o	Hypoglycemia. Renal glycosuria with very low threshold.
	0.5	o	100	220	187	152	122	1.0	o	o	No symptoms. Mild diabetes.
	o	o	90	200	167	130	100	1.5	trace	o	Thyrototoxicosis. Not diabetic.
	1.5	+	170	280	358	312	287	3.5	trace	o	Diabetic symptoms. Moderately severe diabetes.
	trace	o	150	220	230	160	154	2.0	o	o	Obese. Hepatic diabetes. No dia- betic symptoms.
	3	trace	200	383	400	382	296	5.0	+	trace	Thyrototoxic signs. Severe diabetes and thyrotoxicosis.
	3.5	++	250	380	412	380	300	5.0	++	+	Severe diabetes with renal changes.
	1.0	o	85	158	132	110	80	o	o	o	Normal.

FIG. 1.

prick into suitable solution, but it is much more convenient to take a sample of 2 ml. of oxalated blood and transport this to the laboratory. If the blood sugar is high, say above 250 mg. per cent. or higher, a diagnosis of diabetes is certain and suitable steps must be taken for treatment. If the blood sugar value is normal in the fasting state then the presence of diabetes can be practically excluded. Values between 130 mg. and 180 mg. per cent. found up to two hours after a previous meal, leave the diagnosis in doubt.

In most instances it is essential to carry out a full *sugar tolerance test*.

The patient has no food from 8 o'clock on the previous evening. Samples of urine are collected on waking and before the test is started. The latter sample is a true fasting sample, and even in renal glycosuria may be the only sample of urine found completely free of sugar. If this sample contains sugar, diabetes is probable, the only exception being renal glycosuria with very low values of the renal threshold for glucose. A sample of fasting blood is taken and the patient is given 50 g. of glucose in 3 to 4 ounces (85 to 114 ml.) of water. Samples of blood are taken at intervals of 30 minutes for two hours and samples of urine are collected at similar intervals. The sugar content of the blood samples is determined by one of the usual methods (Macleod, Hagedorn-Jensen, Nelson, Folin-Wu) and a curve constructed. Normally the blood sugar does not exceed 170 mg. per cent. and the highest value occurs in 30 minutes. Thereafter the curve returns towards normal fasting value, and reaches this level or just below it within 120 minutes. The great majority of normal persons show fasting blood sugar values below 100 mg. per cent. Only occasionally is this exceeded in the elderly patient.

The following curves with marginal notes illustrate the types of blood sugar in various conditions (fig. 1).

GLYCOSURIA IN DIABETES UNDER TREATMENT

It is important in the continuous control of the diabetic patient under treatment to be aware of the significance of recurrent glycosuria. No diabetic patient under treatment should show acetone in the urine. In ideal circumstances the same should apply to glycosuria, but this degree of normality can seldom be achieved permanently in the severe diabetic under insulin therapy. In the milder obese diabetic in the later decades treated with a low calorie diet and limited carbohydrate, the urine should remain free of sugar, but when insulin dosage over 20 to 30 units daily is in use, permanent aglycosuria is not easily maintained, without risk of hypoglycæmia.

In establishing initial control of the diabetic state, it is essential to realize the time relation of glycosuria to the type of insulin in use.

With a single morning dose of *protamine zinc insulin*, and when the patient is taking an adequate diet, say with 120 g. of carbohydrate, the first sample of urine which should become free of sugar is that passed immediately before breakfast next day, the overnight sample having first been voided. When this sample is found to be free of sugar on several consecutive days, care must be taken in further increase of insulin to avoid hypoglycæmia at this time. In patients under good control with this type of insulin, this sample of urine should always be free of sugar.

THE INVESTIGATION OF TINEA INFESTATIONS

By C. H. WHITTLE, M.D., F.R.C.P.

Physician in charge of Skin Department, Addenbrookes Hospital, Cambridge.

THE fungi causing skin lesions in man are the epidermophyton, the microspora, the trichophyta and the candida. The fungus elements can best be demonstrated by soaking the material, scales or hairs, in 30 per cent. potash between slide and cover-slip for ten minutes and examining under the $\frac{3}{8}$ " and $\frac{1}{8}$ " objectives. A little pressure on the cover-slip may help by thinning and clearing the film. Only the commoner infections will be described: tinea pedis, tinea cruris, tinea capitis, tinea corporis, tinea unguium.

TINEA PEDIS AND TINEA CRURIS

These are caused as a rule by the same species, *Epidermophyton floccosum*.

Tinea pedis ("toe-rot", "athletes foot") is characterized by moist intertrigo of the toe clefts, usually the third and fourth, with maceration of the skin and a tendency to crack in the fold. It is more common in moist sweaty feet in hot weather, and in susceptible subjects is difficult to eradicate completely. The fungus can readily be found in the sodden horny layer, which is removed and examined microscopically in potash. Mycelium, 5 to 10 μ in diameter, may be seen in long branching strands and breaking up into brick-like arthrospores. The organism grows well, but slowly, on beer wort agar at room temperature, giving characteristic colonies.

Tinea cruris (Dhobie's itch) is a marginate scaly lesion, often several inches in diameter, in the fold of the groins or internal fold. The scales show abundant mycelium in potash under the microscope.

TINEA CAPITIS

It is important to remember that tinea capitis is a disease of childhood and in practice is never found in adults, except very rarely as favus (see p. 32). Moreover, in children it dies out spontaneously at puberty. This is because the sebum of the adolescent and adult, male and female, contains substances which inhibit the growth of the microspora usually responsible for scalp ringworm. But it is equally important to recall Whitfield's dictum that every bald scaly patch in a child's head, especially if there are broken hairs present, should be regarded as ringworm until steps have been taken to disprove the diagnosis. The reason for such a dogmatic statement is that microsporon ringworm spreads rapidly and is highly contagious. It is quite useless to pluck out hairs at random and send them to a laboratory for

With a single morning dose of *globin insulin*, the first sample of urine to become free of sugar is that passed about 5 to 6 p.m., the bladder having been previously emptied at about 3 to 4 p.m. When this occurs the diabetic state is coming under control and further modification must be conducted with care. With two doses of soluble insulin (at 7.30 a.m. and 6.30 p.m.) the samples of urine which will first show no sugar are those passed at 12 noon and 12 midnight, the bladder having been emptied an hour previously.

With various combinations of insulin, e.g. protamine zinc insulin plus soluble insulin as one injection, or protamine zinc insulin in the morning and soluble insulin at night, the timing becomes more complicated. The diagram (fig. 2) indicates the diurnal curve of the blood sugar under the influence of insulin and the times at which the urine will be free of sugar.

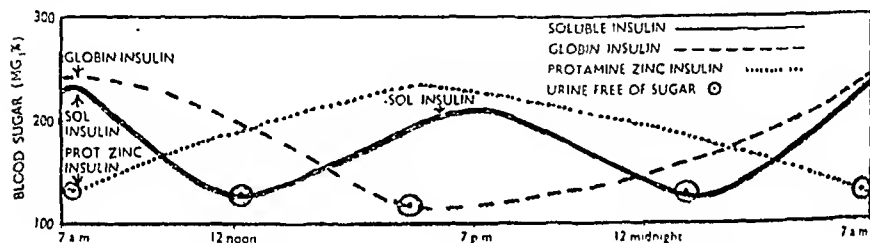


FIG. 2.—Relation of blood sugar to glycosuria under insulin treatment.

An alteration in the renal threshold for glucose would produce considerable modification. With a rise in the threshold, such as commonly occurs in diabetes of long duration, glycosuria could be more easily abolished. When the renal threshold for sugar is low, it may be much more difficult to render the urine free of sugar. This occurs occasionally in diabetes, and if an attempt is made to render the urine free of sugar by increasing the dose of insulin, hypoglycæmia is likely to occur first.

In the untreated case of diabetes the daily amount of sugar passed in the urine may be large, 200 g. or over. In the successfully treated case on insulin, the sugar lost in the urine should not exceed 20 g. daily, an insignificant drain on metabolic resources.

References

- Exton, W. G. (1936): *N.Y.St.J. Med.*, 36, 1545.
 Lyall, A. (1946): *Quart. J. Med.*, 60, 243.

TINEA UNGUIUM (RINGWORM OF THE NAILS: ONYCHOMYCOSIS)

Ringworm of the nails is shown by thickening, discoloration, roughening and breaking up of the nail plate, usually starting in one nail and at the free edge. The organism should be sought in nail clippings, which are teased out with needles and then soaked for several hours in 30 per cent. potash before examining microscopically. Cultures are not always fruitful, but the fungi isolated are usually *Trichophyton mentagrophytes* or *T. rubrum*.

Chronic paronychia is the bolster-like tender swelling of the finger-nail folds seen fairly commonly nowadays in housewives. It is almost always due to infection with candida (monilia), although secondary invasion with septic organisms may occur. The thick-walled, yeast-like budding oval bodies can best be shown by scraping scales from beneath the fold, flattening them between two slides in glacial acetic acid, drying, fixing and staining with weak methylene blue. The organism grows readily at body temperature on plain nutrient agar in twenty-four hours, yielding moist white or pale colonies with a vinegar-like smell; but the differentiation of truly pathogenic strains requires fermentation reactions.

CONCLUSION

No attempt has been made to include all the fungus infections of the skin, or to describe the detailed laboratory methods of investigation, which are considered to be beyond the scope of an article intended primarily for those in general practice.

BLOOD CULTURES

By R. W. FAIRBROTHER, M.D., D.Sc., F.R.C.P.

Director, Department of Clinical Pathology, Manchester Royal Infirmary.

CULTURE of the blood is often an important investigation as, in many infections, it may be the only means of isolating the causative organism and thereby providing not only a diagnosis but also a satisfactory control for chemotherapy. The demands for this investigation have, in consequence, increased considerably in recent years and it is important that the principles of the test should be understood.

The presence of bacteria in the blood stream is a not uncommon phenomenon. They may be found during mild infections or following slight traumatic lesions, such as the extraction of teeth with damage to the blood capillaries. In such circumstances the number of bacteria in the blood is small, their presence is transitory, and they do not produce any obvious clinical manifestation. This condition is often referred to as *bacteriæmia*.

In severe infections the organisms may be present in relatively large

diagnosis: the negative report which follows will merely lull all concerned into a false sense of security. The only materials worth examining are the *broken* hairs or the scales. Broken hairs must be sought carefully and are to be found at the edge of the advancing lesion. The question whether or not they are indeed infected with fungus can often be answered without the aid of a microscope: a little chloroform swabbed over the affected zone reveals the infected hairs by their curious frosted appearance. Wood's light (fluorescence) and the microscope will then confirm the diagnosis. The hair root is broken up and surrounded by a thick mosaic of round refractile spores 7 to 10 μ in diameter. Cultures will usually yield *Microsporon audouinii*, but *M. canis* is quite often responsible for this type of scalp ringworm.

Another less common form is the kerion, a heaped up, circular, *granulomatous* angry-looking lesion which may be several inches in diameter, from the follicles of which pus exudes and hairs fall out. The appearance is highly characteristic, and this is fortunate because the spores or mycelium may be found only after searching several hair roots taken from the diseased follicles. Kerion is usually caused by the trichophyta of animal origin (e.g. *T. mentagrophytes*).

A still rarer form of scalp ringworm is favus, a slowly advancing, less contagious type which may persist into adult life, and which causes alopecia with scarring. The organism is found as mycelium *within* the hair shaft (*Trichophyton*, or *Achorion*, *schoenleini*). Favic scatula are more often than not conspicuous by their absence, and for this reason and the slow evolution of the lesion the diagnosis is often missed.

TINEA CORPORIS

Ringworm of the open skin appears as circular red discs or rings, with scales or vesicles on the active advancing edge. It may be secondary to scalp ringworm (microspora) but is usually of animal origin (*Trichophyton mentagrophytes*). The material selected is the scale, or better, the top of a vesicle, which should be lifted off with skin forceps and mounted upside down in potash. As in other fungus infections of animal origin the finding of fungus elements may be a tedious matter, but the material will usually yield positive cultures in a week or ten days at room temperature. Another form of animal origin is the kerion type affecting the beard region, hands or forearms in adults, or unclothed parts in children. It is much more common in country than in town dwellers.

A third rather uncommon form of tinea corporis is *Pityriasis (tinea) versicolor*. It appears over the trunk in pale-brown slightly scaly sheets, is usually extensive but causes few symptoms. The fine scales contain abundant mycelium, and spores in grape-like branches, which are easily found under the microscope.

necessary in order to isolate the organisms; they should be prepared during a characteristic pyrexial episode.

There are also several *anaerobic infections* in which blood cultures are invaluable. Necrobacillosis, a condition caused by *Bacteroides necrophorus*, is a fulminating infection with multiple necrotic abscesses in the tissues, accompanied by septicæmia. Anaerobic streptococci have also been isolated by blood culture, usually from puerperal infections.

TECHNIQUE

The detailed technique of blood culture is not required here but some of the guiding principles may be considered with advantage. The great variety of conditions in which blood cultures are necessary and the wide range of organisms that may be isolated, indicate clearly that a simple routine technique cannot be adopted for all purposes.

The modern practice is to select a range of media (3 or 4), add various amounts of blood to each, and incubate under the most suitable atmospheric conditions. Methods used for the aerobic bacteria are unlikely to be successful for the anaerobes or micro-aerophilic organisms, and therefore it is necessary to consider the clinical condition of the patient and use the most appropriate technique (Butler, 1937; Penfold *et al.*, 1940). Information about chemotherapy is also essential, as the presence of sulphonamides or penicillin will inhibit the growth of sensitive organisms, and therefore if chemotherapy is being carried out, neutralizing substances must be added to the media.

Cultures should be prepared during a pyrexial period; this is particularly important in the case of chronic meningococcal septicæmia and subacute bacterial endocarditis, when repeated cultures may be necessary before a positive result is obtained.

The blood should, if possible, be collected by the pathologist, but when this is impracticable it is essential to collect and add the blood to the various media with strict aseptic precautions. The medium plus blood provides an excellent food supply for bacteria, and the addition of a few contaminants will produce a heavy growth after incubation. A simple and effective method of collecting blood for culture in general practice is to use a vacuum venule containing a small amount of liquid (Stuart, 1948).

References

- Bramwell, J. C. (1948): *Lancet*, ii, 481.
Butler, H. M. (1937): "Blood Cultures", London.
Cope, S., and Bennett, R. A. (1949): *J. Roy. Army Med. Cps.*, 92, 44.
Fairbrother, R. W. (1947): *Bull. Min. Hlth. pub. Hlth. lab. Ser.*, 6, 180.
Jones, A. M., Herring, R., Langley, F. A., and Oleesky, S. (1947): *Brit. Heart J.*, 9, 38.
Penfold, J. B., Goldman, J., and Fairbrother, R. W. (1940): *Lancet*, i, 65.
Stuart, R. D. (1948): *J. clin. Path.*, 1, 311.

numbers and may persist for some time. This condition has been designated *septicæmia*, but it is doubtful if the organisms actually multiply in the blood stream, except in the terminal stages of a fatal infection; in the majority of cases it represents an overflow of the organisms from the active focus of infection. This condition is associated with a well-marked clinical syndrome.

CLINICAL USES

In some infections, e.g. *enteric fever* and *undulant (abortus) fever*, the organisms are present in the blood during the initial stages of the infection when the clinical signs are vague and indefinite, consisting mainly of pyrexia, headache and general malaise, i.e., cases for which the term "P.U.O." is widely used. Blood culture is an essential investigation and should be carried out as early as possible. It is important to note that if the primary culture is negative and the symptoms persist, the blood culture should be repeated, as in the milder types of these infections the presence of organisms in the blood is intermittent. In enteric fever, the organisms are present in the blood stream during the early stages and are not usually found in the fæces, and possibly urine, until the second week. In the milder forms of the disease, especially paratyphoid infections, organisms may never be isolated from the fæces or urine, and therefore blood culture during the pyrexial period, which may persist for several weeks, is an important diagnostic procedure (Fairbrother, 1947; Cope and Bennett, 1949). It is particularly valuable in persons previously inoculated with T.A.B. vaccine as their agglutination reactions are often of little value. In "abortus" fever, blood cultures are of limited value as the diagnosis can generally be established by serology before the cultural tests are completed.

The clinical features of *bacterial endocarditis* vary considerably. In many cases the diagnosis can be readily established, but in the chronic form, particularly low-grade infections with *Streptococcus viridans*, the diagnosis may present considerable difficulty as there may be long apyrexial periods. Any unexplained pyrexia in a patient with chronic heart disease calls for immediate and, if necessary, repeated blood culture (Jones *et al.*, 1947; Bramwell, 1948).

In severe *pyogenic infections*, such as pneumonia, carbuncles, puerperal fever, and meningitis, septicæmia is a common feature in the absence of effective chemotherapy. Before the introduction of the sulphonamides and antibiotics, blood cultures were required mainly for prognostic purposes, but now they are seldom needed, as the diagnosis of the primary infection can readily be established by other means, and the response to treatment is usually dramatic.

Blood cultures are often of value in *meningococcal infections*, particularly in the septicæmic forms, either fulminating or chronic. In the fulminating form the cultures are almost invariably positive, but in the chronic form, in which the pyrexial bouts are intermittent, repeated cultures may be

COLD AGGLUTININS

In a number of diseases, e.g. atypical virus pneumonia, aplastic anæmia, hæmolytic anæmia, cirrhosis of the liver, and trypanosomiasis, cold agglutinins have been found in the blood serum. This is one form of auto-agglutination, in that blood recently drawn from an individual may agglutinate spontaneously as the temperature falls. The antibodies act best at a temperature of 4°C ., and when warmth is gradually applied the agglutination fades and disappears completely at about 37°C . The agglutination is restored by cooling. The cold agglutinins may cause difficulty in blood grouping. They act on red cells of all the blood groups, and if not properly washed the agglutinin adherent may give rise to the erroneous conception that the cells belong to group AB. This agglutination reaction has been used as an aid to diagnosis in atypical virus pneumonia and other conditions.

BACTERIAL AGGLUTINATION

Agglutinins for various bacteria may also be found in the sera of individuals. These may occur in normal people or may arise as a result of infection, and are usually of low titre. Thus the serum of many individuals may agglutinate an antigen of *B. coli* in a titre of 1/10 or 1/20. The normal agglutinin content of the serum for a particular organism, e.g. *B. typhosum*, depends upon the extent to which the disease produced by the organism is endemic in the population concerned. The agglutinin may be increased as a result of preventive inoculation.

It is important to remember that immunization with a specific organism may lead to the production in the patient's serum of agglutinating antibodies which are specific for the characteristic antigens of that organism. Thus there are somatic (O) and flagellar (H) agglutinins. The agglutination reaction can be employed in two ways. Given an unknown antiserum it is possible that the nature of the antibodies in this serum may be determined by testing its agglutination power with suspensions of known bacteria. Conversely, if from the blood or from the excreta of a patient an unknown organism has been recovered, it is possible that this organism may be identified and typed by testing it with various known artificial sera kept in the laboratory.

AGGLUTINATION REACTIONS IN THE ENTERIC GROUP
OF DISEASES

Certain organisms are known to be capable of producing a continued fever of the enteric type. In this country *Bact. typhosum* and *Bact. paratyphosum* B are almost always responsible. *Paratyphoid A* fever is common in India and the Middle East and *paratyphoid C* fever in British Guiana, but are rarely seen here. Each of the causative organisms possesses a flagellar (H) and a somatic (O) antigen. The serum of a patient suspected of suffering

BLOOD AGGLUTINATION TESTS

By J. BAMFORTH, M.D., F.R.C.P.

Director, Clinical Pathology Laboratories, St. Thomas's Hospital.

THE agglutination tests which may be performed with the blood sera of individuals are concerned for the most part either with the agglutination of red cells or of bacteria. These reactions may be observed under both normal and abnormal conditions.

HÆMAGGLUTINATION

The isoagglutinins occurring in normal sera and the antigens (agglutinogens) of the red cells determine the four blood groups. The abnormal agglutinins which develop in the sera of Rh-negative individuals as a result of the antigenic effect of Rh-positive antigen in red cells introduced from without, have attracted considerable attention during recent years. The agglutination tests concerned with blood grouping and with the Rh factor, however, are outside the scope of this article.

THE PAUL-BUNNELL TEST FOR GLANDULAR FEVER

It was discovered in 1932 that the serum of a patient suffering from glandular fever contains agglutinins for sheep's red cells in high titre. It must be remembered that normal sera may agglutinate sheep's red cells in a dilution of $1/64$, and, rarely, in even greater dilution. In glandular fever the time at which the reaction first appears varies in different cases. In many it is found at the end of the first week, but it is sometimes delayed for a fortnight or more. In a small minority of cases with typical blood picture and clinical features the Paul-Bunnell test is found to be negative even after repeated examination. The strength of the reaction also varies in different cases. A titre of $1/64$ and $1/128$ is suggestive of this infection. The test should be done again to determine the presence of a rise, which if obtained confirms the diagnosis. In most cases, however, much higher titres are found, e.g. $1/512$, $1/1024$ and $1/2048$. There appears to be no correlation between the titre of agglutination and the severity of the infection or the abnormality of the leucocyte picture. In some cases the test may remain positive for some weeks. It is stated that this curious reaction may also be found in patients who have been treated with horse serum, but special procedures have been described to distinguish this reaction from that found in glandular fever. When taken in conjunction with the clinical data, the glandular enlargement and the blood picture, the Paul-Bunnell test is of great value in the diagnosis of this disease.

Vi-agglutination.—It was shown a few years ago that recently isolated strains of *Bact. typhosum* possessed an additional somatic antigen. This antigen, which is probably situated on the surface, is known as the Vi antigen and is associated with virulence. When this antigen is present the organisms are not agglutinated by an O antiserum. By repeated subculture or by heating at 100° C. the Vi antigen is lost and the organism can then be agglutinated by an O antiserum. In patients suffering from typhoid and in typhoid carriers, Vi agglutinin may be demonstrated in the serum. A suspension of typhoid organisms which react only with Vi agglutinins is used. In cases of suspected typhoid fever a titre of 1/10 is regarded as significant, and on repetition a rise in titre may be found. Vi antigen is found also in the paratyphoid bacilli.

Carriers.—The agglutination test may also be very useful in the search for carriers in an epidemic. As an example, in an outbreak of paratyphoid B fever which occurred during the war, three carriers were discovered. One of them had had a mild illness some weeks previously, lasting for about a week, but the other two gave no history of illness whatsoever, and had never been away from work. In each of these cases a flagellar agglutination of 1/500 and more was obtained against the paratyphoid B organism. On examination of the faeces paratyphosum B was isolated from all three cases. In some cases, however, carriers show a low agglutinin content in their serum.

AGGLUTINATION TESTS IN UNDULANT FEVER

Under the generic name *Brucella* are described three organisms, *Br. melitensis*, *Br. abortus*, and *Br. suis*, which are capable of producing undulant fever in man. *Br. melitensis*, which causes infection in goats and sheep, is responsible for undulant fever in man, not only in Malta and the Mediterranean littoral but also in many other parts of the world. *Br. suis*, which produces infection in pigs, is responsible for some of the cases in the United States. *Br. abortus*, the cause of contagious abortion in cattle, is the organism which produces undulant fever in various parts of Europe and in Britain. Here many cases are now being recognized, and although diagnosis by blood culture is preferable, in the majority of cases it is determined by the agglutination reaction of the patient's serum. The three organisms in this group are closely related in antigenic constitution. In this country practically all infections are of the abortus type, and many authorities use *Br. abortus* as the only agglutinating antigen. I think, however, that it is better to use both *Br. abortus* and *Br. melitensis*, as in three cases I have obtained high agglutinating titres for *Br. melitensis*, whilst those for *Br. abortus* were low. It has been shown that an appreciable percentage of sera from persons who drink large quantities of infected milk or who are employed on farms, in milk depots, or slaughter houses, agglutinate *Br. abortus* to 1/40 or over. Most of these cases represent latent infection but there are no clinical signs of undulant fever. There are also a number of mild cases with little rise in

from an enteric fever should therefore be tested against H and O suspensions of each organism likely to be encountered. As a rule, both H and O agglutinins are developed in the patient's serum, but in some cases only one of them is found. It has been shown that some cases of enteric fever may pass through their course without developing H agglutinins whilst developing O agglutinins to a fairly high titre. Sometimes the reverse is found. It has been shown that O agglutination is not so specific as H agglutination. Cases of undoubted typhoid fever (*Bact. typhosum* isolated from blood culture) may give somatic agglutination with *Bact. paratyphosum A* and *Bact. paratyphosum B*, as well as with *Bact. typhosum*. Analogous remarks apply to paratyphoid A and B fevers. It may not necessarily occur that the titre for the infecting organism is higher than the others. H agglutination is more to be relied upon for determining the type of infection.

In the typical case of *enteric fever* the H agglutination reaction usually becomes positive towards the end of the first week. The titre of agglutination rises about the twentieth day to a maximum and then gradually falls, finally disappearing in convalescence. The rise of O agglutination usually precedes that of H agglutination, and the agglutinins are usually present in lower titre. Therefore if the case is first seen early, e.g., on the third day before agglutinins have time to develop, it is advisable to do agglutination tests as well as blood culture. It affords a base line, so to speak, should it be necessary to repeat the tests at a later date.

Normal serum may agglutinate the typhoid and paratyphoid bacilli in low dilutions. In the inoculated patient in the early stages of the disease an H titre of $1/50$ is highly suggestive and one of $1/100$ almost conclusive of typhoid fever. An O titre of $1/100$ is very significant. In any case the diagnosis may be confirmed by repeating the test after an interval of a few days so as to follow the agglutination curve.

In cases previously inoculated with T.A.B. vaccine the position is more difficult. Inoculation gives rise to the development of both H and O agglutinins in the serum, although usually the O agglutinins are of smaller titre and tend to disappear more rapidly. There is, however, considerable variation in the strength of the agglutinins and their rate of disappearance in different subjects. A rise in titre of H agglutinin for one definite organism may be significant, but in many cases infection by one organism may lead to a rise in the agglutination titre for others in the group. Other febrile conditions, notably *typhus fever*, may produce similar results (anamnestic reaction). The H agglutinins are therefore unreliable. The O agglutinins if found in a titre of $1/100$ or more six months after inoculation and showing a rise after a few days are highly suggestive of enteric infection but are not always present. Fortunately, in recent years a considerable advance has been made in the discovery of culture media for the isolation of enteric organisms, especially from the faeces. The desoxycholate citrate agar and the bismuth-sulphite medium of Wilson and Blair are particularly useful. Diagnosis by recovery of the organism is always preferable.

The *Weil-Felix reaction* is not easy to understand. The *Proteus X* bacilli are only found in a very small proportion of cases of typhus. Vaccination with *Proteus X* bacilli affords no protection to susceptible animals subsequently inoculated with typhus. Vaccination of individuals with rickettsia vaccine does not produce agglutinins against *B. proteus*. In addition to typhus, *Proteus X* bacilli have been isolated from the blood of patients suffering from other diseases, e.g. typhoid fever, tuberculosis. The most likely explanation is that this is a group agglutination. It has been shown that *Proteus OX 19* and *R. prowazeki* possess an antigen in common.

AGGLUTINATION TESTS IN BACILLARY DYSENTERY

In the serum of patients with bacillary dysentery, agglutinins usually appear about the tenth day, but in many cases not at all. Often the patient is much better or well on the way to complete recovery before the agglutinins are found, and the reaction is then of no practical value in diagnosis. Moreover, with the introduction of the desoxycholate citrate medium for the isolation of the dysentery bacilli from the fæces the chances of finding the causative organism have been considerably improved, rendering agglutination tests unnecessary. In certain cases, however, the reaction may be of advantage. The three most important organisms which give rise to bacillary dysentery are *B. shigæ*, *B. flexneri* and *B. sonnei*. Other things being equal, the most serious cases are produced by *B. shigæ*.

Shiga dysentery.—Shiga infections are rarely found in this country.

In normal subjects, serum agglutinins for this organism are seldom found, with the result that a titre of $1/25$ is almost conclusive and $1/50$ conclusive of infection. Although there are exceptional cases there appears to be some correlation between the severity and length of shiga infections as shown by the temperature chart and the titre of agglutination. In about 40 per cent. of cases, and most of these are mild, the reaction is absent. In slightly more severe cases a titre of $1/25$ may be obtained; in yet more severe cases, $1/50$. In cases with marked constitutional disturbance and high fever lasting two or three weeks a high titre of $1/100$, $1/200$, or rarely more, may be found.

In some cases which give a temperature chart and a clinical picture resembling enteric fever a high agglutination titre against *B. shigæ* can determine the diagnosis when there has been failure to recover the organism from the fæces. A rising or falling titre occurs during the course of an acute Shiga infection. Shiga cases often show a high Flexner agglutinin content in the serum, apart from a coexistent Flexner infection, which is rare.

In *Flexner dysentery* the interpretation of the agglutination reaction is difficult. In testing for Flexner agglutinins it is advisable to use one or two varieties of the Flexner group as antigens. Many normal sera show an agglutination titre for *B. flexneri* of $1/50$ or $1/100$ and in many cases the results obtained are without significance. There are also many quite mild cases of diarrhœa lasting for only a day or two which yield a growth of *B. flexneri* on culture of the fæces, and from which for the most part low agglutinin titres are obtained. In cases which do show high agglutination

temperature and slight symptoms in which the sera show low agglutination titres. The reaction usually becomes positive at the end of the first week and shows a rising curve. In about 90 per cent. of the cases which I have seen the reaction obtained, usually after the disease has been established for a month or more, has been positive at $1/1000$ or $1/2000$. Cases have been described, however, in which although a positive blood culture has been obtained the agglutination reaction has remained negative. It is estimated by American authors that 10 per cent. of cases show a complete absence of agglutinins. In view of the fact that the clinical picture of undulant fever often shows no striking or distinguishing features it is advisable to include this test in pyrexia of unknown origin as a routine procedure.

AGGLUTINATION TESTS IN TYPHUS FEVER

The classical epidemic louse-borne typhus fever and the various forms of endemic typhus have been shown to be produced by a special group of organisms to which the generic name "rickettsia" has been given. They are very minute organisms which have been regarded as occupying an intermediate position between the viruses and the bacteria, and are found in the alimentary tract of certain insect vectors, e.g. lice, fleas, mites, ticks. Several species have been described, of which *Rickettsia prowazeki* is the cause of epidemic typhus.

In 1916, Weil and Felix cultivated a strain of *B. proteus* from the urine of a case of typhus fever, and found that this organism was agglutinated not only by the serum of the patient but also by the sera of other patients suffering from typhus. Similar strains which were called *Proteus X* strains were grown from the blood or urine of other cases of typhus fever. Of all these strains the *Proteus X*₁₉ was the most agglutinable and an O antigen of this strain is used in the Weil-Felix reaction.

The agglutinins in the serum of the typhus patient appear about the fifth day and increase in titre to about the fifteenth day, when they decrease rapidly and fade away in convalescence. The titres obtained vary in different cases from $1/50$ to even $1/50,000$. Normal sera never give a positive reaction at more than $1/25$. Certain patients suffering from typical proteus infections, such as pyelitis, cystitis, infected wounds, may also give positive agglutination results. When, in a case of typhus, the result of the test is considered with the clinical features of the case there is no doubt as to its value in the diagnosis of typhus. It was found that with certain types of endemic typhus other strains of proteus proved more efficient antigens in the agglutination test than *Proteus OX* 19. In Malaya, two types of typhus are found: the cases occurring chiefly in shops and storehouses (the urban typhus), which react with *Proteus OX* 19, and the cases occurring in the country districts (scrub typhus), which react with *Proteus OX* K. In other types of rickettsial disease agglutinins are found which react with another strain of *Proteus*, namely *OX* 2. Pure suspensions of rickettsiæ, prepared from the lungs of rats or mice, may be used as antigens in the agglutination test instead of *Proteus X* strains, but from the practical point of view there is no advantage.

TESTS OF RENAL FUNCTION

By H. E. ARCHER, M.R.C.S., L.R.C.P., F.R.I.C., Ph.C.

Assistant Chemical Pathologist, St. Bartholomew's Hospital; Chemical Pathologist, West London Hospital.

As a preliminary to embarking on any of the renal function tests it is of the greatest importance that a careful examination of the urine be made, and the emphasis on this is greater now that it has become the fashion to suggest that blood examinations are all-important. Whereas a gross degree of proteinuria accompanied by cells and casts is so obvious in its implications, the assessment of the significance of slight proteinuria is sometimes very difficult, and unless the simple protein tests are carried out with great care much unnecessary subsequent investigation may result. It is often the case that elaborate renal function tests are promoted by a casual preliminary examination of an unsuitable specimen of urine.

Urine for the qualitative protein tests and for microscopical examination for abnormal constituents in its deposit should be fresh, as free from contamination as possible, and in the case of female patients a catheter specimen is generally a necessity. When testing a urine for protein, a knowledge of its reaction is important, as it is easy to miss a small amount of protein in an alkaline urine, owing to the formation of alkaline metaprotein which will not precipitate on boiling, even after acidification. The use of salicylsulphonic acid will avoid this difficulty but should not be relied upon alone, as it may give false positive reactions with some substances, for example, uroselectan or alkaloids, whilst the nature of an unusual type of protein such as Bence-Jones's will not be suspected.

CHOICE OF TESTS

In considering the choice of tests for determining the functional capacity of the kidneys, it is well to review their main normal activities. These are:—

- (1) The excretion of the waste products of metabolism, in which the nitrogenous portion is the most important.
- (2) The regulation of the osmotic pressure of the blood by controlling the salt excretion.
- (3) The regulation of the hydrogen-ion concentration of the blood, and conservation of base by excreting some of the nitrogen of urea in the form of ammonium salts.
- (4) Excretion of unnatural or toxic substances, sometimes in a conjugated form.

titre for *B. flexneri* the results may be significant, but under epidemic conditions care must be taken to exclude infection with *B. shigæ*, which may be the real causative agent. A coexistent rise in Shiga agglutinins does not occur with Flexner infections.

In cases of *Sonne dysentery*, agglutinins are found in the serum of about 50 per cent. of patients. These agglutinins are usually of moderate titre, c.g. 1/200, and disappear shortly, but in chronic cases they may persist for some time.

THE AGGLUTINATION REACTION IN WEIL'S DISEASE

Weil's disease is caused by a spirochæte, *Leptospira icterohæmorrhagiæ*, but a few cases may be caused by *Leptospira canicola*, a closely allied species normally pathogenic for the dog. During the first week of the disease the presence of the spirochætes can usually be established in the blood or spinal fluid by guinea-pig injection. After the first week the organisms are not found in the blood but appear in the urine in increasing numbers, where they may be demonstrated by dark-ground illumination or by guinea-pig inoculation. At the end of the first week, agglutinins begin to appear in the blood and increase in amount, reaching their maximum a few weeks later. Very high titres may be obtained. The agglutinins fade away only very gradually and may be found in appreciable quantity years after the attack is over. In testing the patient's serum the antigen may be formed of living organisms when agglutination is seen in the lower dilutions and lysis of the organisms in the higher. Antigens composed of formolized suspensions are now usually preferred, and agglutination only is seen. One or two strains should be used as antigens, including one of *Leptospira canicola*.

The last case which was investigated in the clinical laboratory of this hospital may prove of interest.

On the fifth day of the disease, when the total leucocyte count was 18,000 per c.mm. with polymorphs 74 per cent., five ml. of the patient's blood and five ml. of the spinal fluid were each injected into the peritoneal cavity of a guinea-pig. The guinea-pig injected with the spinal fluid developed jaundice and died. *Leptospira icterohæmorrhagiæ* was demonstrated in the spleen, adrenal and kidney of the animal. The guinea-pig injected with the patient's blood showed no response to leptospiral injection, in all probability owing to the penicillin treatment given to the patient by his medical attendant. The agglutination reactions, which were kindly done for us by Dr. J. C. Broome, gave the following results: on the fifth day positive 1/100, on the tenth day positive 1/3000, and on the twenty-fourth day positive 1/30,000. The patient made a good recovery.

CONCLUSION

The object of this article has been to point out the value of certain agglutination reactions and the information to be derived from them in several important and interesting conditions. It is possible that in the future other diseases may be found in which they may be of equal value.

This is of particular importance in that it enables the observer to determine if a raised urea is due to renal dysfunction or to extrarenal causes, such as dehydration, cardiac failure, or excessive protein destruction in malnutrition.

By far the best test of the kind is the *urea clearance test* of Van Slyke and his collaborators. It is a simple test requiring no very special preparation of the patient, but to be of value it demands that the timing of collection and the measurement of the urinary specimens be as exact as possible. As part of this often arises in the duties of a busy ward, it may happen that timing of the urine collection is rather vague, and in such cases the results become quite valueless. For this reason, the test should not be done when there is likely to be any doubt about the emptying of the bladder or the correct timing of the specimen collection. In such cases it is much better to rely on a blood urea and a urea concentration test.

The principle of the urea clearance test is to determine what volume of blood could theoretically be swept clear of urea by the kidneys in one minute. In normal individuals, the clearance under maximum conditions is taken as 75 ml. per minute. Under standard conditions it is 54 ml. per minute. The results are usually expressed as a percentage of the average normal. No special preparation is necessary, but gross or prolonged protein restriction should be avoided. The test is best carried out in the morning, and confinement to bed is preferable but not absolutely necessary. Very small volumes of urine introduce considerable error, both in the emptying of the bladder and subsequent measurements, and for this reason a glass of water should be drunk just before the test, and another an hour later.

After drinking the first glass of water, the bladder is emptied and the exact time noted. This specimen of urine is discarded.

At the end of one hour, the bladder is again emptied, the exact time being noted to a minute. This specimen of urine is kept and marked (1). Just after this specimen has been passed, a sample of blood is taken. At the end of the second hour the bladder is again emptied and the exact time noted. This specimen of urine is marked (2).

The blood urea is determined and will represent the mean blood level over the two-hour period. The urine specimens are accurately measured and their urea content determined.

The calculation of the urea clearance is made for each urine specimen, the second serving as a duplicate check on the first. The volume of urine divided by 60 (or whatever number of minutes elapsed from the first to the second voiding) will show the number of ml. of urine passed per minute, and if this is over 2 ml. the calculation is that for maximum clearance (C_m) because the excretion rate of urea is in simple proportion to the volume. If the volume of urine is below 2 ml. per minute, the calculation is that for standard clearance C_s where the urea excretion rate varies, not in relation to the volume per minute, but to its square root. For maximum clearance the calculation becomes:—

$$C_m = \frac{UV}{B}$$

Where U = Urea concentration in mg. per 100 ml.

V = Urine volume per minute.

B = Blood urea concentration in mg. per 100 ml.

TESTS INVOLVING THE DETERMINATION OF THE NITROGENOUS WASTE PRODUCTS RETAINED IN THE BLOOD

These are the determination of:—

- (1) The blood urea (normal 20 to 40 mg. per 100 ml.)
- (2) The non-protein nitrogen (normal 20 to 40 mg. per 100 ml.)
- (3) The blood creatinine (normal 1 to 2 mg. per 100 ml.)

Of these three, the blood urea is of the greatest value, as no particular advantage comes from the non-protein nitrogen to offset its more difficult and time-consuming determination. The blood creatinine rises late in the course of renal failure and, although occasionally requested, I do not consider that it is often of real value.

TESTS INVOLVING THE DETERMINATION OF THE ELIMINATED NITROGENOUS WASTE PRODUCTS IN THE URINE

Here the choice is inevitably urea. As the twenty-four hour excretion will vary with the protein intake, it is better to use the simple and well-tried *urea concentration test* of Maclean and de Wesselow. It is especially useful when the exact timing of the urinary specimens is difficult or when the complete emptying of the bladder is not certain. The test is best carried out in the early morning. No fluid should be taken in the eight hours preceding the test.

At 5.55 a.m. the bladder is emptied.

At 6.00 a.m. the patient drinks 100 ml. of water containing 15 g. of urea flavoured with tincture of orange.

At 7.00 a.m. the bladder is emptied and the whole specimen kept for examination. This is repeated at 8 a.m. and 9 a.m. The three specimens are then measured and their urea content estimated by the hypobromite method.

To be regarded as normal, one of the three specimens should show a urea concentration over 2 per cent. As urea sometimes provokes an excessive diuresis, some allowance for the volume of urine may be made, but this diuretic action has usually passed off by the time the third specimen is reached.

The usual volumes of urine are between 100 and 120 ml. in the first hour, 80 and 100 ml. in the second hour, and 60 and 80 ml. in the third.

If the test is applied to children under twelve years, the dose of urea should be modified to suit their age. This can be done by lowering the dose of urea by 1 g. for each year under twelve and reducing the volume of water in roughly the same proportion.

DETERMINATION OF THE RELATION OF RETAINED WASTE PRODUCTS IN THE BLOOD TO THAT EXCRETED IN THE URINE

Here again urea is the most suitable, and several tests have been evolved to compare the urea level in the blood with the concentration in the urine.

i.e., in the neighbourhood of 1.010.

Concentration test.—The patient has a normal supper at 6 p.m. on the evening before the test. This meal should contain a fair amount of protein and a minimal amount of fluid. After this the patient has no food or drink until the conclusion of the test. Before retiring, the patient empties his bladder and this specimen is discarded. Any urine passed during the night is also discarded. In the morning at about 7 a.m. the first specimen of urine is collected, labelled specimen (1) and the time noted. One hour later the bladder is again emptied and specimen labelled (2). If the patient is ambulatory he is allowed up and a third specimen is collected at the end of another hour.

The specific gravity of each specimen is taken. For the function to be regarded as normal at least one specimen should have a specific gravity above 1.022. Gross proteinuria may give a false high reading of specific gravity. A reasonably accurate correction may be made for this by multiplying the percentage of protein by 0.003 and subtracting this result from the observed specific gravity.

Phenolsulphonphthalein excretion test.—The patient empties his bladder. He is then given 300 ml. of water to drink and 0.6 g. of a sterile solution of phenolsulphonphthalein is injected intramuscularly or intravenously. The bladder is emptied two hours and ten minutes after the injection, and the total amount of dye present is determined by making the urine alkaline and comparing the resulting red colour with a standard solution of the dye. At least 50 per cent. of the dye should be excreted in the two hours and ten minutes (the ten minutes is allowed as the average time for the first appearance of the dye). Its actual time of appearance is not usually determined except in urogenital practice, when catheterization of both ureters may enable the surgeon to detect the time of its appearance from each kidney, and also estimate the relative and total amounts of dye excreted by the two kidneys.

FACTORS INFLUENCING THE COURSE OF TREATMENT AND PROGNOSIS WHILST NOT THEMSELVES STRICTLY TESTS OF RENAL FUNCTION

The alkali reserve.—Normal range = 55 to 77 ml. of CO_2 per 100 ml. of plasma.

Kidney function is influenced by changes in the blood in the direction of either alkalosis or acidosis, and such influence is much more marked in the case of kidneys the function of which is already impaired. For this reason a determination of the alkali reserve or plasma bicarbonate should be made. This is expressed as the number of ml. of CO_2 available at N.T.P. from 100 ml. of plasma. In a case of severe nephritis with marked urea retention, little improvement can be expected by changes in the alkali

This will show the number of ml. of blood cleared per minute under maximum conditions.

As the average normal figure for maximum clearance is 75 ml. per minute the result is expressed as a percentage of this, viz. $C_m \times \frac{100}{75} =$ percentage of normal renal function. In the case of Standard Clearance the calculation is

$$C_s = \frac{U\sqrt{V}}{B}$$

where \sqrt{V} = the square root of the volume of the urine per minute.

The average normal clearance under standard condition is 54 ml. per minute and the result expressed as a percentage of this becomes:—

$$C_s \times \frac{100}{54} = \text{percentage of normal renal function.}$$

The normal range is from 75 to 120 per cent.

Van Slyke and his collaborators, in fixing their figures for standard and maximum clearance, worked on an average body surface of 1.73 sq. metres. As the kidney size will vary with the body size, it follows that for individuals whose body size is greatly varied from the average, e.g. children, dwarfs, and giants, some correction must be made. This correction is made by

multiplying by $\frac{1.73}{A}$ to correct the urine volume when A = the patient's surface area. These corrections are best made by reference to charts in Peters and Van Slyke, "Quantitative Clinical Chemistry", Vol. II, or Harrison's "Chemical Methods in Clinical Medicine", 3rd edition.

In interpretation of the results of a urea clearance test Van Slyke, quoted by G. A. Harrison, suggests that with clearances over 70 the renal function may be regarded as normal. Between 70 and 40 a mild degree of insufficiency exists; from 40 to 20 a moderate deficit, and below 20 a severe degree of renal dysfunction. Uræmic coma is imminent or present if the clearance is below 5.

CONCENTRATION AND DILUTION TESTS

As one of the main activities of the healthy kidney is its ability to produce a very dilute or a very concentrated urine, any loss of efficiency in this direction is an indication of disease. The tests for dilution and concentration are best separated.

Dilution test.—The patient is given no water after midnight. Urine is collected at 7 a.m. and rejected. He is then given 1000 ml. of water to drink and urine is collected each hour until 11 a.m. The volume and specific gravity of each specimen is measured.

All the 1000 ml. is normally excreted in the four hours and the specific gravity of at least one specimen falls below 1.005. In renal insufficiency a smaller volume is excreted and the specific gravity remains relatively high,

EXAMINATION OF THE CEREBROSPINAL FLUID

By D. P. KING, M.D.

Clinical Pathologist, Charing Cross Hospital Medical School.

THE character of the cerebrospinal fluid reflects pathological changes in the central nervous system, so that much information about the anatomical site and the nature of pathological lesions can be gained by chemical and cytological examination of the fluid.

Withdrawal of fluid.—The site of puncture for withdrawing fluid is usually one of the intervertebral spaces in the lumbar region of the spine, but fluid is taken from the cisterna magna or lateral ventricles in special circumstances. There is always a risk that when a needle is introduced into the subarachnoid space infective organisms may gain entry at the same time, and too much stress cannot be placed on the necessity for scrupulous aseptic precautions for these minor operations, whether they are for anaesthesia, diagnosis or therapeutic control. Dry sterilized or autoclaved apparatus should always be used and the surface of the skin where puncture is intended should be painted beforehand with 2 per cent. iodine in 70 per cent. spirit.

Records of the pressure and rate of flow of the fluid may yield valuable information, and the effect on them of compression of the jugular veins is an important examination which should be made at the time of withdrawal (Queckenstedt).

There appears to be some lack of appreciation of the value of the different investigations relevant to particular diseases. A pathologist in charge of a busy department cannot supervise the handling of every specimen from the time it is delivered to the laboratory, so that request forms accompanying specimens should be filled in with sufficient detail to guide the technical staff. Such phrases as "Routine investigations please" should be avoided. When there is doubt about the diagnosis or relevance of particular investigations a short consultation with a pathologist often proves of inestimable value. The following are examinations of widely accepted diagnostic value, but since their relative importance varies from one disease to another, examination of all specimens along exactly similar lines would be both unintelligent and wasteful of time and material.

COLOUR

Normal cerebrospinal fluid is crystal clear and colourless. Any turbidity is usually due to the presence of cells, but it is unfortunately a fact that from

reserve, but many cases occur in which the apparent renal failure is largely due to a marked deviation of the plasma bicarbonate from the normal. For example, the case of a patient with a gastric ulcer who became too enthusiastic in his self-medication with alkaline powders and developed an alkalosis equivalent to 95 ml. CO_2 per 100 ml. of plasma and a blood urea of 300 mg. per 100 ml. The cutting-off of the alkaline medicine resulted in a rapid fall of the blood urea to within the normal range.

Blood cholesterol.—Normal range in plasma = 100 to 220 mg. per 100 ml.

This constituent of the blood varies in many pathological conditions, but in all cases of œdema due to nephritis, and particularly that sometimes described as nephrosis, a high cholesterol is found.

Plasma proteins.—Normal range 6 to 8 g. per 100 ml. of plasma.

When there is gross or prolonged proteinuria, a fall in the total plasma proteins results, and as the loss is largely albumin the normal ratio of albumin to globulin is upset and may be reversed. The determination of the plasma proteins is a guide to the need for replacement therapy in the treatment of the nephritic œdema. Some cases of myelomatosis suspected of nephritis have their true character revealed by the high total protein, 10 to 12 g. per 100 ml., and the very high apparent globulin fraction.

CONCLUSION

Many other and more elaborate tests have been devised; an example of these is the inulin clearance test, which can be an accurate measure of the glomerular filtration capacity, but those already mentioned will yield useful information if interpreted in their proper relation to the clinical picture and the various extrarenal causes that may modify kidney function. As a routine procedure the careful examination of the urine and determination of the blood urea should come first. Because of their simplicity, and because no apparatus other than that for taking the specific gravity is required, the dilution and concentration tests are useful in all circumstances.

If the conditions under which the test can be carried out are suitable, the urea clearance test is of the greatest value, but its prognostic significance is only of value when repeated, and the effects of time and therapy are seen.

For surgical conditions it is often better to use the dye excretion test or the simple urea concentration test, as they will be of help in deciding how far the renal condition complicates the operative risks. After operative procedures, when marked changes may be produced in the alkali reserve and the blood chlorides, the determination of these constituents is of the greatest service in deciding what therapy will help to relieve the strain on the kidneys.

disease and subacute combined degeneration of the cord, which are not inflammatory, do not cause an increase in cells.

Bacterial meningitis may cause a frankly purulent exudate, but in virus infections, syphilis and tuberculosis the number of cells may be only slightly increased. Polymorph leucocytes are present at some stage in tuberculous and virus meningitis but in syphilis the pleocytosis is invariably lymphocytic in character.

Paracentesis of the subarachnoid space, even by an expert, may entail the puncture of a small blood vessel so that blood-stained fluid is drawn off. The number of red cells should be counted to assess the effect of this contamination on the other elements in the fluid. Five thousand red cells per c.mm., for example, indicate only a small degree of contamination and will not materially affect the chemical findings or the leucocyte count.

There should be no difficulty in distinguishing red corpuscles from leucocytes in a counting chamber, but novices are sometimes misled into making a diagnosis of meningitis by such a faulty interpretation. A blood-stained fluid should be centrifuged and if the supernatant fluid has a yellow tinge (xanthochromia) this is clear evidence that blood has been present in the subarachnoid space.

BACTERIOLOGY

Examination of the fluid by the naked eye in a good light will generally make possible a distinction between the turbidity of blood and the turbidity of exudate. When the presence of a leucocytosis is confirmed by microscopical examination it is most important to examine for the presence of bacteria as soon as possible so that correct therapy can be started at once. Pyogenic bacteria are generally numerous but meningococci and pneumococci may be very scanty and difficult to grow. When the presence of either of these organisms is suspected it is a wise plan to use some of the fluid itself as a culture medium by incubating the specimen overnight. The following day will sometimes show a heavy growth of the infecting organism.

A diagnosis of *meningococcal meningitis* can sometimes be made in the absence of microscopical evidence by mixing the supernatant fluid obtained after centrifuging with meningococcal antiserum. The cerebrospinal fluid may contain products of autolysed meningococci and these will react with the homologous serum to give a precipitin reaction.

Tubercle bacilli are usually scanty in *tuberculous meningitis*, and very prolonged search of films of a centrifuged deposit and the characteristically delicate clot is well repaid. Isolation of tubercle bacilli by culture or guinea-pig inoculation may only provide a diagnosis in retrospect. Mixed meningeal infections are very rare and for practical purposes such a possibility need not be entertained.

When no bacteria are found in a specimen which shows the features of an

time to time turbidity is caused by the precipitation of protein by antiseptic fluid used for sterilizing lumbar puncture apparatus. Bacterial contamination is another cause. Quite recently in my laboratory, turbidity was found to be due to masses of yeast spores from a profuse growth of yeast around the rubber washer of what had been assumed to be a clean and sterile universal container, into which the specimen had been collected.

The fluid becomes yellowish in colour after a cerebral hæmorrhage or thrombosis, owing to the hæmolysis of red blood corpuscles and the formation of bilirubin. This change is quite evident twenty-four hours after a hæmorrhage. A comparable colour is sometimes seen in conditions in which circulation of the fluid has been blocked by a tumour or by adhesions above the site of puncture. The colour may then be due to seepage of serum into the fluid, which has been walled off from the rest of the subarachnoid space.

The threshold for the passage of bile pigments across the ependyma of the choroid plexus is very high, and it is only in exceptionally deep jaundice that plasma bilirubin finds its way into the cerebrospinal fluid.

PROTEIN

The total protein of lumbar fluid does not normally exceed 45 mg. per cent., and most of this is albumin. The concentration is lowest in the ventricles, and it gradually increases towards the lower end of the subarachnoid space. There is normally about 3 mg. per cent. of globulin, which is too little to be detected by half saturation with ammonium sulphate (Nonne-Apelt test).

The quantity of protein increases in any inflammatory condition, the percentage figure depending upon the activity of the inflammatory process. Very high figures are sometimes seen when the circulation of the fluid is impeded by adhesions or tumours above the site of puncture. This is particularly true of spinal block. These high figures may be unaccompanied by any pleocytosis or discoloration. There is a rise in the total quantity of globulin *pari passu* with a high total protein, and a positive Nonne-Apelt test is not then of any particular importance. When, however, this test is positive in the absence of any marked rise in total protein it is of great significance, because it is one of the characteristic findings of neurosyphilis.

CELLS

The upper limit for the number of cells in normal fluid is taken as five lymphocytes per c.mm., but in practice there are seldom more than three. When the number reaches a hundred per c.mm., turbidity is just recognizable. An increase in the number of cells is indicative of meningeal irritation and is seen in all inflammatory conditions either in, or abutting on, the subarachnoid space. Conditions such as idiopathic epilepsy, motor neurone

advanced cases, and in early tuberculous meningitis chloride estimations do not give any information of diagnostic value.

SUGAR

Estimation of the glucose content is very important in the differential diagnosis between *virus meningitis* and *tuberculous meningitis*. There is no fall in the concentration in the former, whereas in the latter the figure is usually about half the normal value (75 mg. per cent.). Glucose disappears completely in acute purulent meningitis of any severity, and its re-appearance coincides with clinical improvement. Estimations are a waste of time in conditions such as neurosyphilis, disseminated sclerosis, and subacute combined degeneration of the cord.

THE CONTROL OF STREPTOMYCIN THERAPY

Everybody is satisfied that in early cases of tuberculous meningitis streptomycin may be a life-saving measure, but there is still uncertainty regarding the best way of administering the drug. Controlled investigation is therefore still necessary so that an answer to this important question can be found. The regular and repeated examination of the cerebrospinal fluid is one part of this control. A detailed account of this branch of clinical pathology is quite impossible but the following points are of interest and importance:—

(1) Streptomycin itself, particularly when administered by the intrathecal route, causes an inflammatory reaction which confuses the interpretation of investigations such as cell counts and protein levels.

(2) The concentration of streptomycin in the cerebrospinal fluid remains fairly constant during intramuscular therapy, but a rising concentration may herald regression in a patient's progress.

(3) Tubercle bacilli can often still be isolated from the fluid several weeks after the start of treatment.

(4) Tubercle bacilli become drug-fast after prolonged treatment, but this develops more slowly in the treatment of tuberculous meningitis and miliary tuberculosis than it does in fibrocaseous tuberculosis of the lungs. The fibrous nature of the lesions in the latter condition, which prevents the drug from reaching the infecting organisms in a high concentration, has been offered to explain this phenomenon. Sub-bactericidal concentrations of any antibiotic always favour the development of drug-fast variants.

acute inflammation, *virus meningitis* or *encephalitis* should be considered. The time will come no doubt when it will be possible to isolate viruses as readily as bacteria. Virus infections are generally diagnosed to-day as a result of exclusion of bacterial infections. Fortunately, virus meningitis usually bears a good prognosis, and patients recover without specific therapy.

WASSERMANN REACTION

It is important that the fluid should be as fresh as possible and free from bacterial or blood contamination for the performance of this test. Globulin is usually present in easily detectable amount when the test is positive, because the syphilitic antibody responsible for the reaction is linked with the globulin fraction of the protein. A positive Wassermann is always indicative of actual invasion of the central nervous system by *Treponema pallidum*.

Kahn tests can be performed after some technical manipulation of a specimen but the results are not as reliable as with the Wassermann, and on that account they are not performed when facilities for the latter are available.

THE LANGE TEST

There are only two conditions in which the Lange colloidal gold precipitation test provides information of positive diagnostic value: neurosyphilis and disseminated sclerosis. The test is dependent upon an increase in the relative proportion and type of globulin in the cerebrospinal fluid, and is not often positive unless there is sufficient globulin to be detected by the Nonne-Apelt test. Blood-contaminated specimens cannot be used for the test.

A positive Lange associated with a positive Wassermann is confirmatory of *neurosyphilis*, and by assessing the degree of precipitation with various dilutions of cerebrospinal fluid it is possible to distinguish between tabetic and parietic types of infection. Fluid from patients suffering from *disseminated sclerosis* can give either parietic or tabetic types of precipitation, but of course will give a negative Wassermann.

The colloidal gold solution is difficult to prepare and pathologists do not like wasting it on specimens upon which the test cannot have any diagnostic bearing.

CHLORIDES

The normal chloride content (720 to 750 mg. per cent.) is about 25 per cent. higher than that of plasma. It falls and rises with the blood levels and it is lowered in bacterial inflammation of the meninges. Lower levels may be found in tuberculous meningitis than in acute meningitis from other causes, but there is now general agreement that this is only true in the majority of

Gibbon died on January 16, 1794, in a house in St. James's where now stands the massive building housing the Conservative Club.

Bentinck Street was laid out on part of the field known as the "Clay Pitt", and the houses had not long been built when the great historian moved into No. 7. The picture (fig. 1) shows the street as it was in his time, and the narrow frontage of his house with the door in the centre. At the western



FIG 1.—Bentinck Street in 1851. This illustration is reproduced from the original water-colour by T. Dibdin, which hangs in the offices of *The Practitioner*.

end are the wrought iron gates which shut off the street from Manchester Square. The street took its name from William Bentinck, second Duke of Portland, who died in 1762, when the street was scarcely a year old. It was his successor, the third Duke, who married the daughter of the Duke of Devonshire and assumed the additional surname of Cavendish by Royal Licence in 1801. Gibbon's house remained unchanged until 1870, when the roof was raised two feet and the front stuccoed. It was demolished in 1909, and the present house built on the site.

Gibbon was not the only distinguished resident in this street. Charles Dickens who, after his well-known early adversities, obtained in 1831 the position of Parliamentary reporter at the early age of nineteen, came with his family to live in "Bentinck Street, Manchester Square". His father, that luckless man who was seldom out of pecuniary embarrassment, found himself from time to time in a sponging-house, from which his hard-working son was asked to rescue him. On one occasion, Dickens says: "I own that his

BENTINCK STREET AND MARYLEBONE

A HISTORICAL CAUSERIE

By IVO GEIKIE-COBB, M.D.

WHEN Edward Gibbon sat in his library at No. 7 Bentinck Street in 1772, two doors from where the offices of *The Practitioner* now stand, and picked up his pen to begin the first book of his masterpiece, did his thoughts turn towards Marylebone or was he occupied solely with the history of Rome? As a historian he can scarcely have been blind to the fascination of the little village—later to be referred to as one of the “Western Suburbs”—in which he had chosen to settle. He spoke of his house as standing “between a street and a stable-yard”, and later compared the view unfavourably with that he enjoyed at Lausanne. But he must have loved No. 7, for in a letter to Lord Sheffield he calls it “the best house in the world”.

Gibbon lived in Bentinck Street from 1772 to 1783. At first, as he tells us, he was somewhat lonely: “While coaches were rattling through Bond Street, I have passed many a solitary evening in my lodging with my books. I withdrew without reluctance from the noisy and extensive scene of crowds without company, and dissipation without pleasure”. But this solitude was to give place to wide companionship when the first volume of the “Decline and Fall” achieved immense and immediate popularity. Hume and Robertson had written historical works of a high order, but it remained for Gibbon to give to the world what Freeman called “the grandest of all historical designs”.

The year 1772 and No. 7 Bentinck Street are therefore noteworthy for the birth of this historical masterpiece, and with its publication its author became a literary “lion”. In March 1774, he was elected a member of the Literary Club, and there he found himself among men of his own intellectual calibre. He tells us in his delightful Autobiography that “there were few persons of an eminence in the literary or political world to whom I was a stranger”; and adds, in a footnote, “From the mixed, though polite, company of Boodle’s, White’s and Brooks’s, I must honourably distinguish a weekly society, which was instituted in the year 1764, and which still continues to flourish, under the title of the Literary Club . . . The names of Dr. Johnson, Mr. Burke, Mr. Topham Beauclerk, Mr. Garrick, Dr. Goldsmith, Mr. Fox, Mr. Sheridan, Mr. Adam Smith, Mr. Stevens, Mr. Dunning, Sir Joseph Banks, Dr. Warton and his brother Mr. Thomas Warton, Dr. Burney, Etc., form a large and luminous constellation of British Stars”. Truly a remarkably representative collection of the famous men of that Augustan age.

It was not only in clubs that Gibbon now had companionship. He entertained his friends at No. 7 and “enchanted them by the good natured wit and instructive vivacity of his conversation” (Hayley).

indicated the bifurcation of the river: Domesday spells it Tiburne; whereas in an earlier charter, dated 951, it is spelt Teoburne and reference is made to a grant of land by Offa. At the time of the Norman Conquest the stream divided Tyburn from the neighbouring manor of Lylleston, or Lisson, after which Lisson Grove is named. The road we know to-day as Oxford Street was once called Tyburn Road, and Park Lane was Tyburn Lane. Later, Tyburn Road became the "Road to Redding"; then Oxford Road, not as you might think, because it leads to the University city, but because it bounded the property of Robert Harley, Earl of Oxford, and was so named in his honour (Loftie).

THE MANOR OF MARYLEBONE

The changes in the ownership of the Manor of Marylebone make interesting reading. According to Domesday it contained five hides: the Survey said "three carucates".* There was pasture for cattle and pannage for 50 hogs. The whole was valued at 52 shillings.

The Manor was the property of the Abbey of Barking, but was held on lease by various people until it came into the possession of Sir Reginald Bray, who was Henry VIII's Prime Minister (Dugdale). The name of Thomas Hobson appears about 1503. He seems to have exchanged the manor for Church lands. Queen Elizabeth then let it in 1583 for a yearly rent of £16 11s. 8d. In the year 1611, King James sold the manor for £829 3s. 4d., but this sale did not include the Park. The purchaser was one Edward Forset, from whose family it passed to Sir John Austin, who sold it in 1708 to John Holles, Duke of Newcastle. The purchase price had now risen to £17,500.

Marylebone Park throughout the years had been retained by the Crown; at this time it was partly farm land and partly a village common. One of the leaseholders was a certain Peter Hinde, whose name has been commemorated by the street which is a continuation of Bentinck Street. The lease of the last farm did not expire until 1811.

The Duke of Newcastle was immensely wealthy and possessed one child, a daughter, the Lady Henrietta Cavendish Holles. This fortunate woman inherited her father's estate in 1711. That year her father-in-law, Robert Harley, was created Earl of Oxford and Mortimer, her husband becoming Lord Harley. In 1724, he succeeded his father as the second Earl. Both these noblemen were book collectors in the grand manner, and to them, of course, we owe the valuable Harleian MSS, now in the British Museum, which acquired them for the bargain price of £10,000.

* A hide "is a measure of land, as much as would support one free family and dependents (perhaps about 120 acres)" (Concise Oxford Dictionary). According to Thoroton "carucates and hides were the very same, and contained 100 acres, six score to the Hundred, more or less, according to the stiffness of the soil". "A Norman measure of land as much as could be tilled with a caruca or plough" (New Standard Dictionary).

absence does not give me any great uneasiness, knowing how apt he is to get out of the way when anything goes wrong". In 1836, Charles Dickens married Catherine Hogarth and moved into 48 Doughty Street. He returned to the amenities of Marylebone when he took 1 Devonshire Terrace—one of three houses which stand at the top of Marylebone High Street, close to the eastern approach of the new church.

Another early resident in Bentinck Street was Francesco Bartolozzi, the Florentine artist. He was appointed engraver to George III and was one of the original painter-members of the Royal Academy.

THE FIFTEENTH CENTURY AND BEFORE

The first building in Marylebone, or Tyborne as it was then called, was the old wooden church of St. John the Evangelist, which stood where Stratford Place now joins Oxford Street. There was no building near, which perhaps accounted for the frequent purloinings of its ornaments by the sacrilegious. It is not easy in these days of noise and bustle to visualize the environment of this little wooden church: "a lonely road between grass meadows here dipped into a hollow, and crossed a brawling brook by a bridge under the shadow of a little country church" (Loftie). If to-day you stand by the magnificent premises of His Master's Voice, opposite the equally imposing shop of Messrs. Dolcis, you will notice the dip in the ground by Stratford Place, and your imagination should have little difficulty in conjuring up the bridge which crossed the Tyburn brook hard-by.

By 1400, the little church had "fallen into ruin and decay", and Robert Braybroke, Bishop of London, authorized its demolition and the building of a new church of stones or flints "half a mile higher up the towne". This new church, dedicated to St. Mary the Virgin, remained until May, 1740, when it was demolished and replaced by the "old Chapel".

The Lord Mayor's Banqueting House stood at the lower end of Marylebone Lane, where Messrs. Dolcis's shoe shop now stands. The Corporation of London owned fields on either side of Tyburn brook: and in 1237 a man called Gilbert Sandford was given permission to convey water to the city from this brook. Each year the Mayor and Aldermen inspected the springs, and afterwards took dinner in the Banqueting House. It is a pretty picture which Strype paints of an occasion on September 18, 1562, when the civic fathers visited the conduits; then entered the woods of Tyburn and hunted the hare; dinner next; then they hunted the fox when "there was great cry for a mile and at length the hounds killed him at the end of St. Giles's, with great hollowing and blowing of horns at his death".

Marylebone Lane must have followed much the same course then as it does to-day, for its windings represent the river bed of the old Tyburn. And what an improvement in nomenclature when the manor of Tyburn became known as "St Mary by the Bourne" and its former name was confined to the region of Marble Arch with its grim associations of the Tyburn executions! The origin of the name Tyburn is obscure; perhaps it

of that leafy lane which ran across the quiet fields of Marylebone, where no doubt young couples strolled in the cool of the evening when the day's work was done.

Many people, some famous only in their time, others whose fame is timeless, came to live in Oxford, or Cavendish, Square. To give a long list of names would be wearisome: mention of a few of the residents may not be. Lord Harcourt, whose name is commemorated by Harcourt House—now a large block of flats on the western side—was a successful barrister whose lot it was to prosecute Defoe for his pamphlet "The shortest way with the Dissenters". Between the first Harcourt House and the present mansion-flats the site was occupied by Portland House, the residence of the fifth Duke of Portland, that eccentric recluse whose vagaries gave grounds for the hearing of the fantastic Druce case. Lady Mary Wortley Montagu lived in this Square in 1723. She was the daughter of Evelyn Pierrepont, Duke of Kingston, and the writer of witty letters and biting satires, as well as the woman who introduced inoculation against smallpox into England. To popularize her belief in the protective power of this method she arranged for her daughter to be vaccinated in the presence of three doctors and the family apothecary.

A most dramatic event took place in the house of the Duke of Chandos. That amazing megalomaniac planned to buy all the land between his town house and his country seat of Canons at Edgware in order that he might be able to drive between the two without once passing over land that was not his own. Having amassed a huge fortune as Paymaster, in ways which no doubt would to-day have landed him in the dock—but our ancestors of the eighteenth century were more broadminded when the speculator was a personage—he proceeded to erect a house in Cavendish Square and to build a magnificent country mansion some twelve miles distant. Nothing was wanting to complete his happiness save an heir, and when a son was born his cup of joy was full. An elaborate christening was planned.

"To mark the importance of the occasion everyone who was anyone had been invited; the King and Queen were present in person to stand sponsor for the future Duke. It is not difficult to imagine the scene in the large salon of this Georgian house, which faced Cavendish Square on the south and Chandos Street on the east. It is a pity that no picture exists of this gorgeous assemblage, but perhaps we can-reconstruct the scene. Their Majesties would have had pride of place in the forefront and next to them would have stood the Duke and his Duchess. The guests would be standing in groups, talking to one another and, from time to time, glancing in the direction of Royalty. Now and then a noble lord or lady would leave one group and join another. A hush of expectancy would follow the noise of voices as the moment arrived for the entrance of the chief actor—the baby.

"From what we are told the actual christening was to have taken place in this room, for the conversation is said suddenly to have ceased as the nurse entered with the baby in her arms 'and approached the baptismal font'. The baby's christening veil was raised: the stillness broken by a scream and followed by horrified silence. For those nearest found themselves looking down on a dead baby" ("Of London and the Londoners", by Anthony Weymouth. In the press).

Among other famous people who lived in Marylebone were Nelson,

of that leafy lane which ran across the quiet fields of Marylebone, where no doubt young couples strolled in the cool of the evening when the day's work was done.

Many people, some famous only in their time, others whose fame is timeless, came to live in Oxford, or Cavendish, Square. To give a long list of names would be wearisome; mention of a few of the residents may not be. Lord Harcourt, whose name is commemorated by Harcourt House—now a large block of flats on the western side—was a successful barrister whose lot it was to prosecute Defoe for his pamphlet "The shortest way with the Dissenters". Between the first Harcourt House and the present mansion-flats the site was occupied by Portland House, the residence of the fifth Duke of Portland, that eccentric recluse whose vagaries gave grounds for the hearing of the fantastic Druce case. Lady Mary Wortley Montagu lived in this Square in 1723. She was the daughter of Evelyn Pierrepont, Duke of Kingston, and the writer of witty letters and biting satires, as well as the woman who introduced inoculation against smallpox into England. To popularize her belief in the protective power of this method she arranged for her daughter to be vaccinated in the presence of three doctors and the family apothecary.

A most dramatic event took place in the house of the Duke of Chandos. That amazing megalomaniac planned to buy all the land between his town house and his country seat of Canons at Edgware in order that he might be able to drive between the two without once passing over land that was not his own. Having amassed a huge fortune as Paymaster, in ways which no doubt would to-day have landed him in the dock—but our ancestors of the eighteenth century were more broadminded when the peculator was a personage—he proceeded to erect a house in Cavendish Square and to build a magnificent country mansion some twelve miles distant. Nothing was wanting to complete his happiness save an heir, and when a son was born his cup of joy was full. An elaborate christening was planned.

"To mark the importance of the occasion everyone who was anyone had been invited; the King and Queen were present in person to stand sponsor for the future Duke. It is not difficult to imagine the scene in the large salon of this Georgian house, which faced Cavendish Square on the south and Chandos Street on the east. It is a pity that no picture exists of this gorgeous assemblage, but perhaps we can reconstruct the scene. Their Majesties would have had pride of place in the forefront and next to them would have stood the Duke and his Duchess. The guests would be standing in groups, talking to one another and, from time to time, glancing in the direction of Royalty. Now and then a noble lord or lady would leave one group and join another. A hush of expectancy would follow the noise of voices as the moment arrived for the entrance of the chief actor—the baby.

"From what we are told the actual christening was to have taken place in this room, for the conversation is said suddenly to have ceased as the nurse entered with the baby in her arms 'and approached the baptismal font'. The baby's christening veil was raised: the stillness broken by a scream and followed by horrified silence. For those nearest found themselves looking down on a dead baby" ("Of London and the Londoners", by Anthony Weymouth. In the press).

Among other famous people who lived in Marylebone were Nelson,

Talleyrand, Mrs. Siddons, George Eliot, Boswell, Edmund Burke, Mrs. Fitzherbert, Turner and, of course, Elizabeth Barrett Browning.

MARYLEBONE GARDENS

Until 1700 there were no houses along the Tyburn Road. As the fields gave place to squares and streets and the houses increased in number, more and

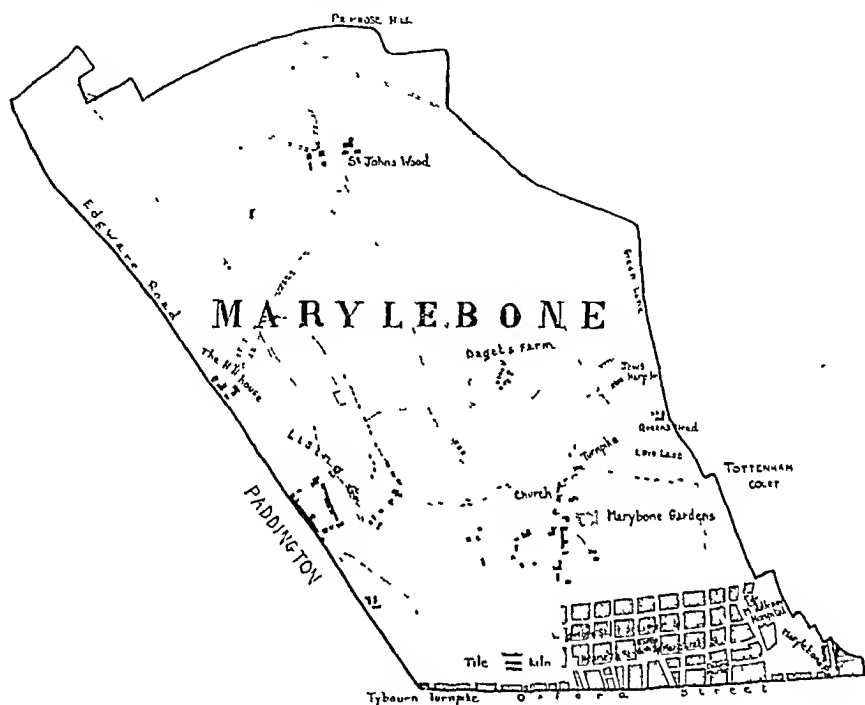


FIG. 3.—Map of Marylebone in 1763.

more people migrated to the district north of Oxford Street. In 1739 there were only 577 houses in the parish of Marylebone; by 1811 the number had risen to 8,476. The growth had largely taken place in the latter half of the eighteenth century. The map drawn in 1763 (fig. 3) shows a few streets only to the north of Oxford Street.

When Gibbon strolled up the High Street in the 1770's what would have met his eye? There were a few scattered houses, but little of interest until he reached the famous Marylebone Gardens (fig. 4). These were situated on the east side of the street and covered the upper end of Beaumont Street, extending to where Harley Street now runs. A picture shows them to have been as attractive as their rival at Vauxhall: but the entertainment was not always as attractive as the scenery. Here took place prize-fights between women who belaboured each other with bare fists. To witness this degrading spectacle, men young and old traversed the fields where now stands the

statue of the great American, Franklin Roosevelt, and crossing the new Oxford Road made their way past the scattered houses to the Gardens. It is some consolation to learn that footpads abounded between St. James's and Marylebone, and that here visitors were often robbed of their valuables.

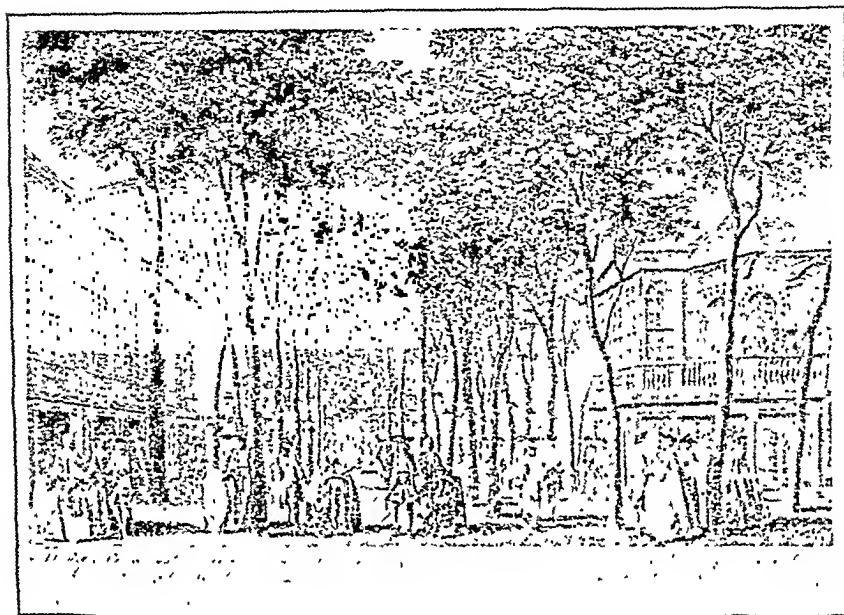


FIG. 4.—Marylebone Gardens in 1755.

(Reproduced from a print in the British Museum)

Indeed, the journey from fashionable London to this "western suburb" was fraught with such danger that the attendance at the Gardens fell in numbers. The proprietor of the Gardens was so disturbed by the consequent loss of revenue that he offered a reward of £10 for the capture of a footpad.

There were, needless to say, other and less horrible spectacles to witness. But Gibbon would not have been present on the famous occasion when Dr. Johnson visited the Gardens to watch the fireworks, for this was in 1784, by which time Gibbon was living in Lausanne. Unfortunately, the evening turned out wet and the proprietor decided not to proceed with the display. The Doctor was very cross and was overheard to say that the postponement was merely to enable the fireworks to be saved for an occasion when more distinguished visitors were present. His remarks being overheard by some young men, a disturbance ensued when they tried to set light to the fireworks. Their efforts, however, met with no success as the rain had made the fireworks too damp to be ignited.

The Manor House which stood at the top of the High Street, almost opposite the old church, was still standing in 1790. It was part of the Park

and was built in the reign of Henry VIII. None of the important personages in Tyburn ever lived here, so far as is known, but it was sometimes used during the reigns of Mary and Elizabeth Tudor as a Royal Palace. In 1703 a school was founded here by a Mr. de La Place. His son-in-law, the Rev. John Fountayne, succeeded him, and it is he who made the well-known *faux pas* to Handel. The two were strolling in the Gardens when the band began to play a new piece. Handel asked his companion to listen to it, as he wanted to know what he thought of it. After some minutes the old clergyman remarked "It is not worth listening to—it's very poor stuff". "You are right, Mr. Fountayne", Handel replied, "it is very poor stuff—I thought so myself when I had finished it".

Pepys liked the Gardens and, in his entry for May 7, 1667, has this to say: "Then we abroad to Marrowbone, and there walked in the Garden, the first time I ever was there; and a pretty place it is". Gay, in "The Beggar's Opera", speaks of Marylebone Gardens as a place for the dissipated; but the bowling-greens were the chief attraction for many. They are referred to in the line, "Some Dukes at Marybone bowl time away". An entry in the diary of John Locke for a date in 1697 mentions the bowling-greens, where the curious stranger "may see several persons of quality bowling two or three times a week all the summer". It seems from records of the seventeenth century, as well as from a map of the Duke of Portland's estate in 1708 (fig. 2), that originally there were two bowling-greens, one behind the Rose of Normandy—then the oldest house in the High Street—the other adjoining the old Manor House. John Sheffield, Duke of Buckingham, was much addicted to this pastime, and also to the alluring vice of gambling, in which he indulged during his visits to the Rose Tavern—a noted gaming-house in the High Street. His parting toast was: "May as many of us as remain unchanged next spring, meet here again". Both bowling-greens later formed part of Marylebone Gardens.

THE HIGH STREET

Thomas Smith, whose "Historical Account of the Parish of St. Mary-le-bone" was published in 1833, tells us this about the High Street: "Being situated in the centre of the Parish, formerly comprised the principal part of the village of Mary-le-bone: the Church, the Royal Palace, the Rose Tavern, and Bowling greens, the splendid Mansion built for the purpose of containing the Earl of Oxford's Library, the Rose of Normandy, and a few detached houses with gardens formed the prominent features of its early days. . . .". It is true that shops and flats have sprung up until the "few detached houses with gardens" have long since disappeared. The only open spaces are those made by Hitler's bombs, which destroyed several houses on both sides of the street. Yet not even this calamity has robbed the "little High" of its friendliness and its character. Let us hope that nothing ever will.

FRECKLES

By E. W. PROSSER THOMAS, M.D.

Physician for Diseases of the Skin, National Temperance Hospital, London.

Ephelides, or common freckles, are small flat pigmentary spots mainly of irregular or serrated outline and of a characteristic yellowish colour. Typical unilateral freckles have been recorded, but their usual distribution is symmetrical with a tendency to grouping in areas exposed to sunlight, namely the forehead, nose, cheeks, backs of forearms and hands, and sometimes the shins; they occur occasionally on covered parts (so-called cold freckles). Freckles are much more common in fair than in dark skins and are mostly correlated with red hair or red-blond hair. The spots become intensified and conspicuous in the summer because of the stimulating effect of ultra-violet light on the formation of pigment. But freckles do not, as is sometimes supposed, disappear completely in the winter; although many have apparently vanished or are visible only as faint stains in ordinary light, their presence can be demonstrated at all times when the skin is examined under ultra-violet light filtered through Wood's glass, which shows up the small circumscribed hyperpigmented areas quite clearly.

Ephelides are not congenital but appear in early childhood, usually between the sixth and eighth years; they tend to diminish with the years. Histological examination of an *ephelis* shows no abnormal changes apart from a simple excess of melanin pigment in localized groups of epidermal cells, mainly of the basal layer.

ORIGIN AND NATURE OF FRECKLES

There is a strong hereditary basis for freckling. For example, in 46 pairs of uniovular twins studied by Siemens (1924) both members were free in 15 pairs and both freckled in 30 pairs, and the degree of freckling was the same in both members of a pair. Only in one pair was one member freckled and the other not. Siemens observed a strong relationship between freckles and red hair but found scarcely any between freckles and the colour of the iris. Freckles are not rare with black-brown hair; these persons, however, may be genetically red-haired but have the red pigment masked by excessive quantity of melanin (Cockayne, 1933). The direct descent of freckles has been noted in many cases; for example, for five generations in one pedigree (Meirowsky, 1919). In a marriage between a freckled and an unfreckled parent the expectation of freckled to unfreckled children appears to be 1:1, and in that between two freckled parents it is 3:1. Cockayne regards freckling as probably due to a single dominant gene which is linked with that for red hair, both being in the same chromosome.

The nature of freckles is in dispute and the literature is confused. Darier regarded them as in every way comparable with *nævi*, despite their not being classed as such by the majority of authors. Meirowsky (1942) believes that the former distinction between freckles and *nævi* is *not justified* and that freckles represent the simplest form of pigmented *nævus*: the term *nævi* including all diffuse or circumscribed anomalies of the skin which are inherited, become visible at various times of life, and are composed of elements, such as pigment, blood vessels, lymph vessels, non-striated muscles, nerves, glands and hair, which are quite normal in themselves but are abnormal in their proportion. Thus, no sharp differentiation is possible between common freckles, *nævi spili* (flat pigmented moles) and lentigo, and from the anatomical point of view there is a gradual evolution from the feebly pigmentary freckle to *nævus spilus* and from that to the most striking hairy, warty and molluscoid moles. Meirowsky affirms that the normal, excessive or deficient manifestation of the single elements of normal skin, as well as microscopical *nævoid* features, are all determined by the germ plasm.

DIFFERENTIAL DIAGNOSIS

Even if both ephelides and superficial lentigines are simple *nævoid* pigment hypertrophies, there are well-marked clinical differences between the two which are not sufficiently recognized in some dermatological textbooks. Lentigines, which are present in almost everyone, appear much earlier in life than do freckles—usually in the second and third years—and are small annular or lenticular macules more deeply pigmented and of more regular outline. All are familiar with the isolated flat facial lentigo—the so-called beauty spot. Lentigines occur in dark as well as in fair skins and their pigment is fixed and independent of sunlight, although some intensification may take place in the summer. In contrast with freckles, lentigines are discrete and of haphazard and asymmetrical distribution, occurring on covered parts of the body, such as the trunk and genitalia, as well as on exposed areas. The various differences between ephelis and lentigo have been enumerated by Brown (1943), who has studied the incidence of lentigines in children and discusses their possible significance, especially in regard to their appearance, sometimes in profusion, after infections in early childhood, such as pertussis, common colds, broncho-pneumonia, sinusitis and otitis media. He ascribes juvenile superficial lentigines to temporary toxic damage to the adrenals with consequent disturbance of melanin formation.

Histologically, superficial lentigo, like ephelis, consists of a loading of epidermal cells in a circumscribed area with melanin pigment, but in deeper lentigines there is in addition some thickening of the epidermo-dermal junction with proliferation of the rete ridges and also evidence of an inflammatory reaction in the cutis.

Apart from the scattered pigmentary spots which occur sometimes in the elderly on the face, neck and dorsa of the hands in association with involutionary changes in the skin, there is a special and fortunately rare type of lentigo known as *lentigo maligna*, which appears usually, but not exclusively, in later life. Malignant lentigo, which was described by Hutchinson under the name *infective melanotic freckles* and later by Dubreuilh as *melanose circonscrite precancereuse*, usually occurs on the face and at first resembles an ordinary flat, very dark lentigo. But instead of the hyperpigmentation remaining localized and stationary it extends peripherally, and satellite foci of pigmentation often appear in the adjacent skin. Eventually the lesion becomes proliferative, vegetative and vascular, constituting a pigmented carcinoma which metastasizes by lymphatic spread to the regional lymph nodes or *via* the blood stream to distant organs.

Malignant lentigo requires early and wide surgical excision with minimum manipulation of the tumour—removal with the line of excision close to the edge of the lesion is inadequate and dangerous. Neither this nor any other variety of flat or slightly raised smooth pigmented mole should be treated with acids, carbon dioxide snow, electrolysis or electro-desiccation.

TREATMENT

Freckles have been regarded from ancient times as a cosmetic defect. In some places it was believed that they could be cured by transfer to animals or to other persons and the various herbal and other folk-lore remedies employed for their removal ranged from a decoction of Solomon's seal made into soap to the application of the saliva of a fasting person (Rolleston, 1940).

Modern treatment is hardly more satisfactory because no applications to the surface can permanently remove pigment deposits within the skin, except at the cost of producing a scar. Freckle remedies and bleach lotions contain mild irritants which aim at exfoliating the horny layer and thus mechanically removing surface pigment in the scales. The chemicals employed for this purpose include ammoniated mercury, 3 to 8 per cent.; mercuric chloride, 3 to 6 per cent.; lactic acid, 0.5 to 1 per cent.; potassium hydroxide, 0.5 to 1.5 per cent.; and salicylic acid, 3 to 6 per cent. Other remedies consist of oxidizing agents, such as hydrogen peroxide or the perborates, incorporated into creams with the object of bleaching the melanin, but these probably act also as exfoliatives and have little bleaching effect. According to Schwartz and Peck (1947), the monobenzyl ether of hydroquinone will prevent the formation of melanin in the portion of skin to which it is applied, but takes from two weeks to two months to act because the melanin already present must be cast off before the skin loses its colour. A cream containing 2 to 5 per cent. of hydroquinone monobenzyl ether may be used for whitening a large area, or smaller areas may be

painted with the same percentage in collodion. Allergic contact dermatitis may result from the use of this chemical and also from the skin-peeling agents.

A formula for a so-called bleach freckle lotion is:—

Potassium chlorate	15 grains (1 g.)
Potassium carbonate	60 grains (4 g.)
Borax	15 grains (1 g.)
Glycerin	120 minims (7.2 ml.)
Water, enough to make	3 ounces (85 ml.)

Although there is no satisfactory means of eradicating freckles completely, their exaggeration in the summer can be prevented to some extent by screening them against sunlight with so-called sunshade preparations. It must be remembered that skin pigmentation is increased by rays of different wave-length from those causing erythema; hence *suntan* preparations, which filter out the sunburn rays but allow the longer pigment-forming rays to pass, are useless for preventing freckles. For example, the darkening of freckles cannot be prevented by applying *p*-aminobenzoic acid ointments and lotions, which are effective against *sunburn*. All heavily pigmented cosmetics (liquids, creams or powders) will prevent or reduce the passage of ultra-violet rays, or a "sunshade" ointment such as the following can be tried:—

Calamine	15 per cent.
Lanolin	12 per cent.
Yellow soft paraffin	38 per cent.
Water	35 per cent.

In freckled persons there is an aberration of the pigmentary properties of the skin as a whole, so that under the influence of sunlight only the small freckled areas acquire pigment, the intervening skin responding either with a feeble production of pigment or with none. Thus the non-freckled areas of skin become red and irritable in bright sunlight and such persons should avoid undue exposure and should not as a rule receive artificial ultra-violet treatment. It should be noted also that freckles are aggravated by other forms of radiation, such as X-rays, and on the whole indicate a generally sensitive skin.

References

- Brown, E. E. (1943): *Arch. Derm. Syph., Chicago*, 47, 804.
 Cockayne, E. A. (1933): "Inherited Abnormalities of the Skin", London, p. 67.
 Meirowsky, E. (1919): *Arch. Derm. Syph.*, 127, 143.
 — (1942): *Brit. J. Derm.*, 54, 104.
 Rolleston, J. D. (1940): *Ibid.*, 52, 77.
 Schwartz, L., and Peck, S. M. (1947): "Cosmetics and Dermatitis", New York, p. 62.
 Siemens, W. H. (1924): *Arch. Derm. Syph.*, 147, 210.

THE A.B.C. OF GERIATRICS

By TREVOR H. HOWELL, M.R.C.P.Ed.

*Lecturer in Problems of Old Age, St. Bartholomew's Hospital;
Consulting Physician, Bermondsey Mission Hospital;
Physician, Geriatric Unit, St. John's Hospital, Battersea.*

DURING the past year, Regional Hospital Boards all over the country have encountered the problem of the aged and chronic sick. Old age is now medical news. Following the report of a committee set up by the British Medical Association ("The Care and Treatment of the Elderly and Infirm", 1946), it has become fashionable to advocate the setting up of "Geriatric Units" to deal with the aged and infirm. This, however, is more easily said than done. There are few doctors with special knowledge of disease in old age: there are no nurses specially trained to care for the elderly. In the past, neglect has been the common lot of the chronic sick. This cannot be changed overnight, even by the magic directives of the Minister of Health himself.

Since definition should precede disquisition, it is well to begin by saying that geriatrics is more a state of mind than a branch of medicine or a mode of treatment. It is a reaction against the belief that after sixty a patient is too old to be medically interesting or therapeutically rewarding. Nearly all those who hold this faith have, at some point in their career, been suddenly faced with the necessity of providing medical care for a large number of elderly sick or infirm patients. The result of this experience has been similar, whether the subject was originally physician, surgeon or general practitioner.

THE SPECIAL PROBLEMS OF OLD AGE

The first stage of the geriatric philosophy is the discovery that the ordinary methods of medicine and surgery can be applied successfully to elderly patients. Once diagnosed, pneumonia can respond to sulphonamides as well at eighty as at eighteen, albeit rather more slowly. Dyspepsia due to a gastric ulcer may occur at seventy-seven and be treated by the same methods as those used for a patient of twenty-seven. Intestinal obstruction in a man of sixty needs the same type of operation as if it had been found at the age of sixteen. This is the stage of glorious justified optimism which affects brave young men with therapeutic vigour. But after this comes the discovery that everything is not so simple as they had expected. Old age has its problems of degeneration and decay which do not yield to routine methods. The stiff, contorted joints of chronic arthritis need more than heat and salicylates; the chronic bronchitic wheezes and coughs in spite of elegant expectorant mixtures; the hemiplegic grows flexed and helpless, with red pressure points steadily declining into sloughing bed-sores, no matter what drugs are given. Realization of this impasse constitutes the

second stage of geriatrics. The third follows naturally—segregation and study. Let the sheep which can be treated successfully be separated from the goats which do not respond. Then concentrate on the latter. It was in this way that Miss Marjory Warren evolved her techniques for managing incontinence and rehabilitating hemiplegia. It was in this way that Cosin altered the prognosis of a fractured femur. It was in no other manner that progress was made in treating chronic arthritis at St. John's Hospital, Battersea. Collect your cases for comparison, then get down to thought and experiment, trial and error. Eventually one lesson at least will be learnt—what *not* to do.

From this description of geriatric evolution it can be seen that insistence on active treatment, the desire for classification of patients, painstaking personal attention to small points in management, and great persistence are the essentials of those who would care for the aged and chronic sick. Add to this an interest in the methods of physical medicine and occupational therapy, which are so necessary in cases of long-term sickness. Experience of elderly patients who have passed from doctor to doctor and from hospital to hospital will sooner or later evoke the cry: "Why didn't we get this case sooner?" This leads to a wish for contact with the earlier stages of disease. In consequence, the hospital physician will start an out-patient clinic for old folk. After a time he discovers that many elderly sufferers are not able to walk from their homes to the clinic. The natural reaction to this finding is to transport these patients to the hospital by ambulance, so that they, too, can have the benefit of out-patient consultation and physiotherapy. This leads, sooner or later, to an interest in the home conditions of elderly people and the social services which can be utilized to assist them. Almoners, social workers, Red Cross, W.V.S., "meals on wheels", home helps, and the like, are enlisted to aid those who cannot gain admission to the wards. If the practitioner has any curiosity left, he wants to visit the patients in their own homes to see what kind of life they lead. Thus domiciliary visits are eventually added to the services of what was originally a purely hospital unit.

Of course, anyone who is really interested in this type of work wants to know what other people are doing for their elderly patients. The budding geriatric worker starts to visit other units and picks the brains of those in charge. He may beg, borrow or steal quite a lot in this way. The occupational therapy department at the West Middlesex Hospital fills him with envy; the physiotherapy aides trained at Orsett Lodge, Essex, give him ideas on saving manpower; the remedial exercise classes at St. Helier Hospital, Carshalton, Surrey, hint at possible developments. If he joins the Medical Society for the Care of the Elderly, he may see new techniques demonstrated and explained in meetings at Liverpool, Leeds, Redruth, and elsewhere. The American journals of geriatrics and gerontology introduce him to new world views on old age. In consequence, the care of the elderly and chronic sick, which was once considered a dull, dreary, unrewarding

occupation, now becomes an actively advancing branch of medicine, with almost endless possibilities.

Once the doctor has thus become enthusiastic, his nursing staff cannot help becoming infected. The old attitude "keep them in bed and keep them quiet" goes by the board. When a ward sister hears of the achievements of Isleworth, Bermondsey, or Belmont Road, Liverpool, she wants to see them for herself. A visit to another Geriatric Unit gives her a taste for competition. Local patriotism is aroused and the nurses are stimulated to "keep up with the Joneses". In this way, the morale of the wards increases and patients formerly considered past treatment are galvanized into activity. After a time, there will be so many patients up and about that the unit looks more like a convalescent home than a place for treating disease.

THE AFTER-TREATMENT PERIOD

Some of the old folk go back to their families when treatment is finished. Others have no one to take them, nowhere to go. Those patients who do not require treatment accumulate and begin to create a problem of their own by preventing other cases from entering hospital. It becomes essential to dispose of them. A few may be willing to enter the local public assistance institution, but many refuse. So, with the aid of an almoner, the geriatric physician now has to start the search for an outflow tract through which he can get rid of patients. If there is a branch of the National Old People's Welfare Committee close to the hospital, he is lucky. This body can often assist by finding homes for the elderly and by visiting them. They may run a hostel, but are usually unwilling to admit any person who may break down in health. Nevertheless, they are always sympathetic and helpful to those interested in old age.

The pressing need for proper disposal of those whose treatment is finished is one of the consequences of the recent legislation emanating from the Ministry of Health. As yet, no satisfactory solution has been found. Liverpool and London wish to create "half-way houses" in which patients may remain under supervision and be introduced to life outside hospital. Leeds has developed a ring of satellite hostels around the unit. Cornwall uses public assistance accommodation in conjunction with hospital beds, under the auspices of a joint committee. But none of these can be considered as the complete answer to the problem. And until discharge of patients is no longer difficult, admission of cases needing treatment cannot be expedited. If this bottle-neck is to be overcome, patients must be taken into hospital from their homes at the stage of their disease when it will still respond to treatment. It should then be possible to return them whence they came within a relatively short time. Early diagnosis and prompt therapy are the only insurance against masses of bed-fast old folk blocking hospital and institution beds for years on end. It is the old adage that "a stitch in time saves nine" which must now be applied to geriatrics.

CURRENT THERAPEUTICS

XIX.—SYMPATHOMIMETIC ACTION AND ITS ANTAGONISM

By W. MELVILLE ARNOTT, T.D., M.D., B.Sc., F.R.C.P.Ed., M.R.C.P.

William Withering Professor of Medicine, University of Birmingham.

THE modification of physiological action by chemical exaltation or depression of adrenergic action provides one of the most useful fields for drug therapy. Any consideration of the pharmacological action of adrenaline resolves itself largely into a study of the distribution and functions of the postganglionic portion of the sympathetic nervous system, for adrenaline (or something very like it) is the chemical agent released at these nerve endings. The only exception to this general rule is in the case of sympathetic fibres to sweat glands and certain vasodilator fibres to voluntary muscles which act by releasing acetylcholine. Indeed, the anatomical division of the autonomic nervous system into sympathetic or dorso-lumbar and parasympathetic or cranio-sacral portions is now largely replaced by the physiological differentiation into adrenergic and cholinergic. The only other important action of adrenaline is that of potentiating acetylcholine, thus improving conduction in the central nervous system, in autonomic ganglia, and at voluntary muscle nerve endings. The medulla of the suprarenal gland, itself formed from the same portion of the neuro-axis as the sympathetic nervous system, may be regarded as a master adrenergic organ capable in emergency of releasing into the circulation enough adrenaline to produce a mass adrenergic action, thus fitting the animal for fight or flight.

Apart from the naturally occurring laevo-isomer of adrenalin found in the adrenal medulla there is a large number of similar compounds, some, like ephedrine, of vegetable origin but mostly synthetic (*l*-adrenaline itself can be synthesized), which have pharmacological actions generally similar but showing important quantitative differences in the various departments of sympathomimetic activity, thus providing opportunity for selective therapeutic action. These drugs with adrenaline action are known as the sympathomimetic amines. Chemically they are all similar in that they have a uniform basis of a benzene ring joined through two carbon atoms to an aminic radicle. The range of compounds shows a variety of combinations and permutations of hydrogen, hydroxyl, methyl, propyl and halogen groups attached to the five bonds (table 1). Something of the order of two hundred different compounds are known, all displaying in some respect or other sympathomimetic action; however, only about half-a-dozen of these are in anything like regular use although many others have been marketed under a variety of trade names, but have never achieved wide popularity.

ACTION OF ADRENALINE

Before considering the differential action of these amines it is necessary briefly to review the action of adrenaline itself. As nearly all these actions are identical with those of sympathetic nerves, they comprise in some sites constriction of plain muscle, in others muscular relaxation. Both actions are apparently effected directly on the muscle itself, and persist and may even be enhanced after degeneration of the postganglionic neurone. The fact that

TABLE I
MOLECULAR STRUCTURE OF SYMPATHOMIMETIC AMINES
(after GADDUM)

Name of Amine	(1)	(2)	(3)	(4)	(5)
Adrenaline ..	OH	OH	OH	H	CH ₃
Nor-adrenaline ..	OH	OH	OH	H	H
Epinephrine ..	OH	OH	H	H	CH ₃
Neo-epinephrine ..	OH	OH	OH	H	CH(CH ₃) ₂
Phenylephrine ..	OH	H	H	CH ₃	H
Norphenylephrine ..	OH	H	H	CH ₃	CH ₃
Ephedrine ..	H	H	OH	CH ₃	CH ₃
Amphetamine ..	H	H	H	CH ₃	H
Methamphetamine ..	H	H	H	CH ₃	CH ₃

the same substance causes some muscle fibres to contract and others to relax constitutes one of the as yet unsolved mysteries of muscular contraction. It is also necessary to remember that whilst adrenergic action may be comparatively constant and clear-cut on the isolated organ or tissue, the results may be complex and variable in the intact animal, as there it represents the resultant of constriction at one site and relaxation at another. Furthermore, the concentration in which it reaches its various sites of action profoundly alters the effect, so that dosage influences the response. The method of administration greatly influences the effect, as its powerful local vasoconstrictor influence delays its absorption, -e.g. subcutaneous injection, even in comparatively large doses produces relatively slight and protracted general effects, whereas a small fraction of that dose directly into the blood stream may produce an almost explosive general reaction.

Effects on the cardiovascular system.—Adrenaline causes constriction of the plain muscle of the vessels of the skin and splanchnic area and relaxation of the muscle arterioles and coronary vessels. The aggregate effect of this is to raise both systolic and diastolic pressures, although in many individuals this

may be in large part off-set by the vasodilating reflexes mediated from the pressure-sensitive receptors in the carotid sinuses and the aorta. On the heart, adrenaline produces four important actions: (1) It accelerates the pulse rate, an action which again may be greatly inhibited or even reversed by vagal inhibitory reflexes. (2) An augmentation of the contractile force of the heart which results in increased cardiac output even in the absence of increase in pulse rate. This effect is well demonstrated in intact healthy humans by the intravenous infusion of a few gamma, a dosage insufficient to produce any of the other cardiovascular effects. (3) An increase in atrio-ventricular conductivity such as may temporarily correct heart block. (4) An increase of the irritability of heart muscle such as may induce ectopic beats, paroxysmal tachycardia or even ventricular fibrillation.

The effect on the *pulmonary blood vessels* of man is not at all clear but it seems that large doses cause a great elevation of pulmonary blood pressure and, in toxic doses, pulmonary œdema. Shrinkage of the spleen with mobilization of the splenic blood lake is another effect. The aggregate effect of all these actions is to effect a redistribution of blood to provide an ample supply to heart and voluntary muscle in preparation for emergency activity.

Effect on bronchial muscle.—Adrenaline inhibits the tonus of bronchial muscle causing a widening of the air passages.

Effect on the alimentary tract.—The general effect is to cause inhibition of peristalsis with a tendency to relax spasm.

Other actions.—Glycogenolysis with elevation of blood sugar and even glycosuria is a useful action. Adrenaline causes a mysterious elevation of the metabolic rate. On the eye it acts as a mydriatic but does not elevate intra-ocular tension. Stimulation is the principal respiratory effect in man. Marked inhibition of tonus in the muscle wall of the urinary bladder may make the act of micturition difficult and inconclusive.

ABSORPTION AND FATE OF ADRENALINE IN THE BODY

Adrenaline is stable in weak acids but in neutral or alkaline solution it is readily oxidized to a pink indole compound. Little absorption occurs from oral doses, although even by this route an appreciable effect can be obtained from doses of the order of 15 mg. given in acid solution and stabilized with glycine. As already noted, its absorption from hypodermic, and to a less extent from intramuscular, injection is very slow because of its intense local vasoconstrictor effect; nevertheless, this is by far the best route of administration, as the action is prolonged and some protection against an excessive dose is secured. Subcutaneous administration in oily solution is used to prolong the action. It disappears rapidly from the blood stream due to cellular fixation where it is quickly inactivated by enzyme action. Personally, I have been much impressed with how easy it is to administer adrenaline intravenously in very dilute solution (1:100,000) at a rate insufficient to produce any appreciable response, whereas an increase of infusion rate by a fraction of a millilitre a minute may be sufficient to produce effects—a

sharpness of end point reminiscent of an *in vitro* chemical titration. Small quantities of an ester of adrenaline appear in the urine.

As would be expected from a substance in constant physiological activity the response to repeated doses in no way diminishes the reaction; indeed, if given at short enough intervals, summation occurs. Adrenaline is incapable of acting as an antigen.

OTHER SYMPATHOMIMETIC AMINES IN GENERAL USE

The closer the molecular configuration is to that of adrenaline the closer is the similarity in pharmacological action. In listing the more important of the amines the sequence is based on increasing divergence from the chemical structure of adrenaline.

Nor-adrenaline.—This compound has no practical therapeutic differences from adrenaline; it is, however, of considerable fundamental interest as it may be formed normally at certain sympathetic nerve endings and may, in fact, be identical with "sympathin E" and "liver sympathin".

Epinine was one of the earliest analogues to be synthesized. It possesses about one-tenth of the pressor activity of adrenaline but is more stable, and solutions can be sterilized by boiling without loss of activity.

Isopropyl-nor-adrenaline has approximately ten times greater power than adrenaline to relax bronchospasm, much less effect on the circulatory system, and is free from any stimulant effect on the central nervous system.

The following preparations not possessing the catechol molecular configuration are more stable, permitting of effective oral administration and prolonging the action.

Paredrine.—In respect of pressor effect this product is intermediate in action between adrenaline and ephedrine; no appreciable influence is exerted on the central nervous system and it has little effect as a bronchodilator.

Pholedrine resembles adrenaline in its low toxic effect on the heart and ephedrine in its prolonged action. It has a marked capacity for restoring blood pressure depressed by surgical shock and in this respect is regarded as one of the most tractable of the sympathomimetic amines.

Ephedrine.—This is one of the most widely used members of this group. Although originally isolated in 1887 from the plant *Ephedra equisitana* (Ma Huang), and therefore preceding by some eight years the discovery of adrenaline, it is only since 1924 that it has achieved wide recognition. It is now almost exclusively of synthetic origin. Its great merit lies in its suitability for oral administration and its relatively protracted action. Its action is very similar to that of adrenaline except that it exerts a pronounced stimulating action on the central nervous system, insomnia being the most troublesome minor toxic reaction; in susceptible subjects it may produce a mild anxiety state. It has recently been discovered that ephedrine exerts a local anæsthetic effect. Injected intrathecally it is also capable of producing anæsthesia, and a surgical operation has actually been performed with no other anæsthetic than 50 mg. of ephedrine. This effect appears to be quite

independent of any vasopressor effect, and it sheds a new light on its well-known capacity to potentiate the anæsthetic action of the cocaine alkaloids. One of the mechanisms whereby ephedrine exerts its action is in virtue of its capacity to act as a substrate competitor for an enzyme which destroys adrenaline, thus rendering the organism more sensitive to adrenaline, whether released from the adrenal medulla or locally at nerve endings. Ephedrine is excreted unchanged in the urine.

Amphetamine (benzedrine) is volatile and is therefore peculiarly suitable for exerting a vasoconstrictive action on the nasal mucosa, thus reducing the turgescence of infective or allergic inflammation. As the sulphate it is suitable for oral administration, when it exerts a comparatively powerful cerebral stimulant effect which renders the subject insensible to fatigue, alert and capable of prolonged mental effort which, however, does not extend to the highest integrative effort such as is necessary in advanced mathematical problems. Appetite is inhibited. It has a medullary stimulant effect superior to nikethamide in its capacity to antagonize narcotic poisoning. Relaxation of gastro-intestinal tonus is produced, but it is useless for bronchial relaxation; indeed, there is some evidence that it constricts bronchial muscle.

Methedrine has similar actions.

THERAPEUTIC USES OF THE SYMPATHOMIMETIC AMINES

The cardiovascular system.—The powerful vasopressor effect of the group finds application in *acute circulatory collapse* such as is associated with surgical shock; the effects are somewhat ephemeral, however, and must rapidly be followed by other measures, such as transfusion, which aim at restoring the blood volume. For this purpose the amines with less transitory action are superior to adrenaline.

The prevention or correction of the hypotension that may complicate *spinal anæsthesia* provides a much more satisfactory opportunity for these drugs. Paredrine, in 10 mg. doses intramuscularly, and pholedrine in the same dosage by the same route, have each a satisfactory effect. In spinal anæsthesia, ephedrine hydrochloride is widely used to combat hypotension and is most valuable when given intravenously in doses of about 50 mg.

In *acute arrest of the previously healthy heart*, such as may occur in accidental asphyxia or during operations under general anæsthesia, adrenaline injected directly into the cavity of the heart or, better still, into the ventricular wall, has for long been credited with the capacity to restore cardiac rhythm: 0.5 to 1 mg. (0.5 to 1 ml. of 1:1000 solution) introduced through a long thin needle inserted into the heart at the inner end of the 4th left interspace. If possible, cardiac massage should also be performed.

Ephedrine sulphate, in 30 mg. doses orally thrice daily, is often beneficial in *heart block*: it improves conduction in the A-V bundle and stops Adams-Stokes' attacks when these are due to intermittent A-V dissociation. None of the other amines is commonly used for these direct cardiac effects.

Local vascular effects.—The intense local vasoconstrictive effect of

adrenaline and like substances is of great value in local anæsthesia, both infiltrative and regional, in that it delays the absorption of the procaine, thus enhancing and prolonging its local anæsthetic effect and diminishing the chances of any toxic action. When used to infiltrate the tissues the addition of a sympathomimetic amine results in a comparatively bloodless field. In general, there is no good reason for employing any other substance than adrenaline for this purpose.

Another local vascular effect which is of clinical value is the shrinkage of congested nasal mucosa, as in coryza, allergic rhinitis, or as part of the induction of topical anæsthesia for nasal surgery. Adrenaline itself is rather too powerful for this purpose in that the vasoconstriction may be so severe and protracted as to result in ischæmic tissue damage. Ephedrine in a 1 to 3 per cent. solution is useful for this purpose. Paredrine may also be used.

There is a wide range of proprietary products, too numerous for individual mention, in which one or other of these agents is conveyed by an oily or isotonic buffered vehicle and applied either by a dropper or atomizer. The oily preparations have the disadvantage that they have been known to set up a lipoid pneumonia. Amphetamine, being volatile, is useful in reducing nasal congestion and the benzedrine inhalant is much used to palliate the discomfort of coryza. However, if more than two inhalations per hour are taken, unpleasant effects such as mydriasis, dryness of the mouth, mental tension and insomnia may occur.

Bronchodilatory action.—The sympathomimetic amines are the most effective agents in overcoming the bronchoconstriction due to hypersensitivity states such as asthma. The effect is largely due to relaxation of bronchial muscle and also to the correction of mucosal congestion. For a quick action, adrenaline by injection is the most effective, but ephedrine orally, in 30 to 60 mg. doses, exerts a more protracted effect although some degree of tolerance necessitating an increase of dose is readily produced. Neo-epinine, in 20 mg. doses, is readily absorbed from underneath the tongue and is an effective bronchodilator.

Cutaneous hypersensitivity reactions.—Such dermal allergic reactions as occur in serum sickness, urticaria, and angioneurotic œdema can be more or less favourably influenced by several of the sympathomimetic amines, particularly adrenaline and ephedrine. How they act is not clearly understood, although their effect may well be due to local vasoconstriction, thus counteracting the vasodilatation of histamine which seems to be an active agent in these pathological reactions.

Stimulation of the central nervous system.—An effect of this nature is minimal with adrenaline and the amines closest to it in structure, but becomes pronounced with ephedrine and is the predominant effect of amphetamine. There seems to be a certain reciprocity between vasopressor and central excitant actions, ranging from adrenaline at one extreme to amphetamine at the other. Another curious feature is that whereas the lævo compounds of adrenaline and its close analogues are more active, in the case of

amphetamine the greater activity is displayed by the dextro compounds (amphetamine B.P. is a *d-l* mixture).

During the late war amphetamine (20 mg.) was employed in healthy subjects to *diminish fatigue* and *increase mental alertness*, although such advantage is at the expense of subsequent enhanced fatigue.

In *psychiatric disorders* amphetamine sulphate is much used. Narcolepsy may be entirely controlled by 2.5 to 10 mg. up to four times a day. A similar dosage may be useful in the symptomatic treatment of depressive states, whilst in the alcoholic it may alleviate the "hang-over" state and counteract the depression of enforced abstinence.

Amphetamine is probably the most useful of the drugs used in *the treatment of obesity* in that it diminishes appetite and has the less important effect of causing a slight increase in metabolic rate, although its continued use in this and other conditions may result in some nausea, abdominal cramps and irregularity of bowel action.

Action on the urinary bladder.—The capacity of ephedrine to relax vesical muscle tonus, thus rendering less insistent the desire to micturate, is employed in nocturnal enuresis. Its action, is, of course, purely palliative and on its cessation relapse occurs.

Although the study of the many varieties of sympathomimetic amines has been a brilliant chapter in the correlation of molecular structure and pharmacological action, in routine practice there is no clear evidence of the superiority of any amines other than the "big three"—adrenaline, ephedrine and amphetamine.

ANTAGONISM

Certain substances, such as ergotoxine, ergotamine and yohimbine, have long been known to antagonize some adrenergic effects, particularly the stimulating actions. This activity probably depends upon the structural similarity of these drugs to adrenaline, enabling them to compete successfully for attachment to the cellular receptors. A hydrogenated form—dehydroergocornine—of the four constituent alkaloids of ergotoxine promises to be particularly useful as a sympathicolytic agent (Goetz, 1949).

Fourneau and Bovet in France have recently developed a group of compounds which, although they resemble the sympathetic amines less closely, probably block adrenaline in a similar fashion. Dibenamine is representative of this group, and one of its striking actions is the prolonged antagonism (three to four days) of the vasopressor effect of adrenaline. There are obvious therapeutic possibilities in this action, but certain toxic effects necessitate further research.

References

- Gaddum, J. H. (1948): "Pharmacology", 3rd edition, London, p. 199.
 Goetz, R. H. (1949): *Lancet*, **i**, 510.
 Gunn, J. H. (1939): *Brit. med. J.*, **ii**, 155, 214.
 Tainter, M. L. (1941): *J. Amer. med. Ass.*, **116**, 2769.

REVISION CORNER

THE ESTIMATION OF HÆMOGLOBIN

It is necessary to emphasize at once that accuracy in hæmoglobin estimations can only be achieved by meticulous care in the dilution of the blood. With the small quantities of blood usually used, faulty technique may cause errors of 10 per cent. From a freely flowing source, the pipette should be filled to the mark, without including bubbles, the tip carefully wiped clean, and the blood rinsed into the diluent. Overfilling of the pipette will cause high results by the addition of blood clinging in the bore above the graduation.

A number of hæmoglobin derivatives have been recommended, but King *et al.* (1948a) have shown that there is little to choose between the common ones. The making of the solution is, however, only one part of the estimation; the maintenance of a suitable standard and their mutual comparison are equally important. A few of the most common methods will be discussed from this point of view.

THE HALDANE METHOD

The test solution of carboxyhæmoglobin is readily made if coal gas is available. Standard tubes calibrated by the National Physical Laboratory are obtainable and are permanent for years if kept cool and in the dark; moreover, they may be re-calibrated at any time. Conditions for matching are not good and the possible errors (which are at least ± 10 per cent.) have been exhaustively discussed (e.g. Macfarlane, 1945). During matching the positions of test and standard should be continually interchanged and two values should be noted: when the test is just perceptibly darker, and just lighter, than the standard. The average of these values is the hæmoglobin concentration.

Conversion into absolute values should be done by the relationship 100 per cent. Haldane = 14.8 g. Hb/100 ml. as determined by King *et al.* (1947).

THE SAHLI METHOD

There are two main difficulties in this method. The first is the continuous deepening of colour in the test solution over a period of several hours at room temperature, which makes it necessary always to match at a given time after mixing. The other difficulty is the standard, which is often a brown glass or gelatin. Some of these do not provide a good match for the test, some are of dubious permanence, whilst many give values which are not in accord with modern determinations. Tests have shown (Macfarlane *et al.*, 1948) that even when using a single instrument the results are not as reproducible as those of the Haldane method.

THE M.R.C. GREY WEDGE PHOTOMETER

This is a new visual instrument described by King (1947) which may be used by daylight or with an electric light attached (manufactured by Keeler Optical Products, Ltd., and sponsored by the Medical Research Council). Two separate light paths traverse the instrument, in one is placed a square section glass cell containing the blood pigment, whilst the other path passes through a segment of an annular grey wedge. This may be rotated so that the density of grey is varied. The two beams of light illuminate the halves of an optical field, which is observed through an eyepiece containing a green light filter. In use, the wedge is rotated until the two halves of the field match, the result is then read from a scale attached to the wedge and calibrated directly in Haldane percentage. Although the wedge is calibrated in this way, the substitution of other filters enables the photometer to be used for other colorimetric estimations, such as blood sugar and blood urea.

The pigment which is used is oxyhæmoglobin, since the difficulty of maintaining a standard is overcome by utilizing the standard properties of the grey wedge. Oxyhæmoglobin is the simplest derivative to prepare, being made by simple dilution of blood with a weak solution of ammonia. Moreover, several investigations (King *et al.*, 1948a; Bell *et al.*, 1945) have shown that it is capable of giving accurate results.

The field conditions for matching in this instrument are good, and it gives accurate and consistent results (King, Wootton, *et al.*, 1948b), the average errors being about one-third of those of Haldane estimations.

PHOTO-ELECTRIC COLORIMETERS

No excuse is needed for including this section since these instruments have recently become cheaper, more readily available and more robust, and they are rapidly establishing a place in every clinical laboratory. Since a definite scale reading is obtained with a given solution, there is a natural tendency to "calibrate" the instrument by establishing a relationship between scale reading and hæmoglobin, henceforth using this relationship to determine hæmoglobin directly and without reference to any standard. Considerable experience has convinced us that this practice is unsafe, and that such a relationship is liable to show changes if the calibration is repeated at intervals. These remarks apply also to instruments which are supplied ready "calibrated".

The only safe method is to use these instruments merely as accurate comparators of test and standard solutions which have closely similar absorption spectra. Alterations in the instrument will then affect test and standard alike. Two suitable methods are recommended:—

(1) Alkaline hæmatin (Clegg and King, 1942), using the permanent inorganic salt solution devised by Gibson and Harrison (1945) as standard. The spectrum of this solution closely matches that of the alkaline hæmatin test.

(2) Cyanhæmatin (King and Gilchrist, 1947), using a cyanide solution of crystalline hæmin as standard. Results show that this method is the most accurate of all the colorimetric estimations tested.*

* Descriptive pamphlets setting out these methods in full can be obtained from British Drug Houses Ltd., who also supply the Gibson-Harrison standard and crystalline hæmin suitable for the cyanhæmatin standard.

I. D. P. WOOTTON, M.B., B.Chir.

References

- Bell, G. H., Chambers, J. W., and Waddell, M. B. R. (1945): *Biochem. J.*, 39, 60.
 Clegg, J. W., and King, E. J. (1942): *Brit. med. J.*, ii, 329.
 Gibson, Q. H., and Harrison, D. C. (1945): *Biochem. J.*, 39, 490.
 King, E. J. (1947): *Ibid.*, 41, xxxii.
 —, and Gilchrist, M. (1947): *Lancet*, i, 201.
 —, —, *et al.* (1947): *Ibid.*, ii, 789.
 —, —, *et al.* (1948a): *Ibid.*, ii, 563.
 —, Wootton, I. D. P., *et al.* (1948b): *Ibid.*, ii, 971.
 Macfarlane, R. G. (1945): *Spec. Rep. Ser. med. Res. Coun.* no. 252.
 —, King, E. J., Wootton, I. D. P., and Gilchrist, M. (1948): *Lancet*, i, 282.

THE USE AND ABUSE OF CALCIUM

CALCIUM salts have a wide range of therapeutic applications. Some of these are rational and successful, others have no definite scientific sanction and are of doubtful efficacy.

Dietary requirements.—The recommended daily allowance of calcium for children is 1 g., rising to 1.4 g. for adolescents; that for adults is a little less than 1 g., but

1.5 to 2 g. is necessary in pregnancy and lactation. The best dietary source is milk, of which one-and-a-half pints provide 1 g. For optimum growth and for the formation of good teeth in children, and for the protection of the maternal bones and teeth against the demands of the fetus and of milk production, ample intake of calcium and vitamin D must be assured.

PREPARATIONS AND ADMINISTRATION

The chief calcium salts and preparations in the B.P. are: calcium chloride, 10 to 30 grains (0.65 to 2.0 g.); calcium carbonate, calcium lactate, calcium gluconate, each 15 to 60 grains (1 to 4 g.); calcium mandelate, 30 to 60 grains (2 to 4 g.); injection of calcium gluconate (10 per cent), 10 to 20 ml, intravenously or intramuscularly. There are also 5-grain (0.32 g) tablets of calcium lactate (in this dosage a convenient placebo).

For oral administration, to increase calcium intake, calcium lactate (13.6 per cent. Ca) and calcium gluconate (9 per cent. Ca) are well tolerated and readily absorbed. Calcium chloride is liable to cause nausea and vomiting; it is much too irritant to be given intramuscularly and extravasation during intravenous administration may cause necrosis and ulceration.

For parenteral use injection of calcium gluconate is much to be preferred; intramuscular injection is usually well tolerated (although necrosis of muscle has been reported after massive doses given to infants). When given intravenously the rate must be slow—at least 5 minutes for 10 ml.—and the injection should be stopped at once if the patient complains of flushing, or a sensation of heat in the tongue or discomfort in the chest. If used at all in the digitalized patient, parenteral calcium preparations demand great care in administration, or synergism may cause serious toxic effects (sometimes fatal).

Oral administration of calcium (dietary or medicinal) should be accompanied by adequate vitamin D. Two teaspoonful of cod-liver oil, one teaspoonful of the cod-liver oil compound of the Ministry of Food, or suitable proprietary capsules can provide the daily intake of 800 units which suffices for prophylactic dosage for all normal children and all adults.

DEFECTIVE CALCIFICATION

In the prophylaxis and treatment of *rickets* and *osteomalacia* vitamin D in adequate dosage should be combined with ample calcium in the diet (milk and milk products). If in *osteomalacia* sufficient milk is not available or tolerated, medicinal calcium is indicated in doses up to 120 grains (8 g) of calcium lactate or gluconate three times daily. In treating *rickets*, supplementing the diet with calcium gluconate has been advised to prevent the occurrence of tetany which may follow the rapid utilization of body calcium for calcification.

Diseases which may secondarily give rise to rarefaction of bone, such as *steatorrhœa*, *hyperparathyroidism*, *hyperthyroidism*, require, in addition to the specific treatment of the disease, adequate calcium and vitamin D intake. In *hyperthyroidism* the daily calcium requirement may be twice the normal or more, and this should be supplied to patients on medical treatment or in the pre- and post-operative phases of surgical treatment.

Rheumatoid arthritis and *osteitis deformans* (Paget's disease) also are associated with a negative calcium balance and undue loss of bone calcium. Adequate calcium and vitamin D intake should be ensured but there is no clinical evidence that very large doses of either or both are of special benefit. *Senile osteoporosis* shows no radiological improvement after increased calcium and vitamin D sufficient to produce a positive calcium balance, prophylaxis throughout earlier life is probably

the only satisfactory treatment. In bone diseases with grossly disturbed ossification of unknown etiology, such as *osteogenesis imperfecta*, large doses of calcium and vitamin D are ineffective.

TETANY

Acute tetany associated with a low serum calcium level may occur with *rickets* or in *lactation*, in *steatorrhœa*, in *hypoparathyroidism*, and in *uræmia*. For severe symptoms the immediate specific treatment is by injection of calcium gluconate (10 to 20 ml.) intravenously (slowly), or intramuscularly, or both; the injection may be repeated in a few hours. Calcium chloride orally (or ammonium chloride) has a slower effect in raising the serum calcium which is due to the acidosis produced.

Chronic tetany, as in *hypoparathyroidism*, is treated by a moderate intake of dietary calcium supplemented by calcium lactate or gluconate, 240 grains (16 g.) or more, daily. This may further have to be accompanied by massive doses of vitamin D (50,000 units or more, daily, as calciferol). Careful supervision of the patient is required to avoid toxic effects, which may include metastatic calcification of arteries and kidneys. The biochemical control is by a simple test of urine samples for calcium excretion and by serum calcium estimations.

Alkalotic tetany due to *vomiting* seldom requires parenteral calcium administration but responds to treatment of the salt depletion state by saline fluids. Tetany due to *excessive doses of alkali* requires cessation of the drug and ample saline fluid administration. The tetany of hyperventilation alkalosis, seen in *hysterical over-breathing*, is stopped by inhalation of air containing 5 per cent. of carbon dioxide, and thereafter sedatives and psychiatric management of the patient are necessary.

TOXIC CONDITIONS

In *acute lead poisoning*, especially with severe abdominal colic, intravenous calcium gluconate is indicated to aid removal of lead from the blood by deposition in the bones; the injection may need to be repeated four-hourly. If symptoms are less urgent, the intramuscular route may suffice, or even oral administration (60 grains [4 g.] t.d.s.). A high calcium intake is an important prophylactic measure which reduces lead absorption.

Calcium compounds have also been used as antidotes in poisoning with oxalates, fluorides, cadmium, and carbon tetrachloride. In overdose with parenteral magnesium sulphate (in treating eclampsia) intravenous calcium is indicated as the pharmacological antagonist. The reported beneficial actions of parenteral calcium gluconate in hepatitis and in eclampsia have not been confirmed clinically.

GASTRO-INTESTINAL SYMPTOMS

Calcium carbonate, e.g. 15-grain doses (1 g.), has been used as an antacid, alone or in suitable proportion (such as 1:1) with magnesium compounds to neutralize the purgative effect of the latter. In aromatic powder of chalk (B.P.), 10 to 60 grains (0.65 to 4 g.), and chalk mixture (B.P.C.), $\frac{1}{2}$ to 1 fluid ounce (14.2 to 28.4 ml.), the chalk is used for the symptomatic relief of *diarrhœa*, often as vehicle and adjuvant to opium preparations. For antispasmodic action in *intestinal* and *biliary colic* parenteral calcium gluconate has been reported effective.

URINARY TRACT DISORDERS

Calcium chloride, 15 to 30 grains (1 to 2 g.), orally, acts as a diuretic and causes acidification of the urine. Calcium mandelate has a similar action and also causes excretion of mandelic acid which is effective in the treatment of some *chronic urinary infections* which have failed to respond to sulphonamides. Fluid restriction is required and the urine must be kept very acid (pH less than 5.3, confirmed by

repeated tests with indicators). Calcium mandelate (50 grains [3.3 g.]), four times daily) may suffice to give the required acidity; if not, it must be supplemented by small doses of calcium chloride, or more commonly ammonium chloride.

Parenteral calcium gluconate has been stated to relieve *renal colic*; it is also used in treating *acute epididymitis*.

VASCULAR AND ALLERGIC CONDITIONS

Although calcium ions are essential for normal clotting of blood, deficiency of these is seldom, if ever, a factor in hæmorrhage encountered clinically. The few apparent successes from the administration of calcium in *hæmoptysis* and *epistaxis* should be regarded as coincidental. By promoting assimilation of iron, calcium may assist in recovery from anæmia following hæmorrhage. In *purpura hæmorrhagica* and in *hæmophilia* calcium is useless.

In various exudative and allergic conditions in which undue capillary permeability may be present, calcium compounds have been used therapeutically but on rather dubious scientific evidence and with, at best, inconstant results. The most common of these is *chilblains*, which have been treated with oral calcium lactate, 30 to 60 grains (2 to 4 g.) t.d.s., and vitamin D, or even by parenteral calcium gluconate. Many cases show no improvement but a few appear to be notably relieved. *Serum sickness*, especially with skin eruptions, *urticaria* and *purpuras with allergic concomitants* have also been treated with similar results.

TUBERCULOSIS

There is no indication for supplementary calcium in *pulmonary tuberculosis*, but the diet should be adequate in calcium as in all other respects. The favourable results from the treatment of *lupus vulgaris* by massive daily doses of vitamin D are achieved without any more calcium than is provided by an adequate diet.

In *intestinal tuberculosis*, the diarrhœa, colic and tenesmus are relieved by parenteral and oral calcium administration.

J. W. CHAMBERS, M.B., B.Sc.

NOTES AND QUERIES

Erythrocyanosis Crurum

QUERY.—I should be grateful for your advice in the following case. The patient is a young girl in good general health, but subject to chilblains. In addition, the lower third of the back of the legs becomes deeply cyanosed in cold weather. The chilblains disappear with the advent of warmer weather, but the disfiguring purple patches remain throughout the summer. Is it likely that administration of nicotinic acid or menaphthone, or exposure to ultra-violet rays, would prove beneficial?

REPLY.—*Erythrocyanosis crurum puellarum*, which has also been called silk stocking disease, is one of the conditions included under the broad heading "perniosis." It is usually seen in girls with some excess of adipose tissue on the legs, and the factors in such are (1) a constitutional susceptibility to cold in which the smallest arterioles contract readily on exposure and do not readily relax on warming; (2) the excess of fat which insulates the peripheral

venules from the underlying deep arteries. Excessive fat, however, is not always a part of the picture, when factor (1) may be said to operate alone. Nicotinic acid is of no value in this condition and the same may be said of vitamin K. On the other hand, wearing fleece-lined boots and warm stockings in cold weather mitigates to a certain degree. *Erythrocyanosis crurum* tends to disappear in adult life but unfortunately permanent enlargement of the smallest veins in the area concerned is a not uncommon sequel. Nicotinic acid may be helpful for the chilblains, but warm covering and plenty of exercise are better remedies.

G. B. DOWLING, M.D., F.R.C.P.

Winter Resort for Vasomotor disturbance

QUERY.—A patient of mine, aged sixty-eight, has diabetes mellitus requiring about 50 units of insulin a day. He has emphysema with recurrent respiratory catarrh, and a blood pressure

of about 170/92. There is no pulsation in the dorsalis pedis or posterior tibial arteries, and he has absent ankle jerks and impaired touch sense in his feet. In the cold weather he gets unhealthy looking shallow ulcers over some of the bony prominences of his feet, and I have several times been obliged to put him to bed on this account. In the same season his chest is troublesome. In the warmer months he has few symptoms. He ought, I feel, to spend the coldest season out of this country, and although not rich he could afford to live quietly abroad during the winter. Can you advise me to what suitable areas he could go, free from currency restrictions; or refer me to any article or other source of information?

REPLY.—Although the ulceration is mainly due to degenerative changes in the nervous and vascular systems incidental to diabetes, vasomotor disturbances also play a part, as is evident from the influence of cold weather. For this reason, considerable benefit might be expected from residence during the winter in a warm dry climate, and I consider Assouan (Upper Egypt) the most desirable that I have ever experienced between the months of October to March, by which time return to this country could reasonably be appropriate. Incidentally, this climate would be most advantageous for the respiratory conditions. Madeira, the Canaries and the Azores are also suitable, but my first choice would be Assouan if the longer journey can be undertaken.

SIR ADOLPHE ABRAHAMS, O.B.E., M.D., F.R.C.P.

Cupralein in the Treatment of Trigeminal Neuralgia

QUERY.—Can you give me any information on the use of cupralein in the treatment of trigeminal neuralgia?

REPLY.—Cuproallyl-thiourea-sodium-benzoate is now being used in the treatment of trigeminal neuralgia. It is manufactured in America under the trade name of cupralein and in this country under the trade name of cuprelone (Bayer). It is at present undergoing therapeutic trials, and preliminary reports suggest that it is of some value. Campbell (*Lancet*, 1948, ii, 690) gave it to thirteen patients, with alleviation of pain in ten. Of these ten, at least one had remained free of pain for a year. My own very limited experience has, however, been less encouraging. It is given intravenously in doses of 50 or 100 mg. in sterile water or saline. In some cases a single injection is all that is required. Others may need as much as 800 mg. over a period of six weeks. In these doses toxic effects are unlikely. With larger quantities renal damage or leucopenia are pos-

sible complications. It is as yet too early to say what place it will eventually take in the treatment of trigeminal neuralgia. But, even if it has to give way later to the tried remedies of injection and root section, it is relatively harmless and worth trying.

S. PRICHARD, M.C., M.B., M.R.C.P.

Toxæmic Albuminuria and Pregnancy

QUERY.—In a patient with a history of toxæmic albuminuria of pregnancy, on what criteria other than normal blood pressure and no albuminuria can it be decided that it is safe for the patient to go through a further pregnancy?

REPLY.—It is not clear from the question whether the patient is now pregnant again or whether she merely wishes to know if it would be safe for her to become pregnant in the future. If pregnant, she has probably sought advice as soon as she realized that she was pregnant. If her blood pressure remains normal and the urine albumin-free, the pregnancy can safely be allowed to continue. The blood pressure should be taken and the urine tested every month until the twenty-eighth week, then every fortnight until the thirty-sixth week, and then weekly until she goes into labour. If the blood pressure rises or oedema occurs she should be confined to bed until the oedema subsides and the blood pressure returns to normal. If albumin appears in the urine, specialist advice should be sought as termination of the pregnancy may require consideration.

If the patient is not yet pregnant, but would endeavour to become so if pregnancy were not contraindicated, further investigation is advisable. The blood urea should be ascertained. A catheter specimen of urine should be examined for casts. Tests of renal function—water concentration, urea clearance and urea concentration tests—should be carried out. If these are satisfactory, pregnancy is permissible, but strict antenatal supervision would be essential.

ANTHONY W. PURDIE, F.R.F.P.S., M.R.C.O.G.

Thorium-X Therapy in Tinea Unguium

QUERY.—I shall be grateful for any information you can give me on the use of thorium-X in the treatment of ringworm of the nails.

REPLY.—Thorium-X is of no value in treating ringworm of the nails. Irradiation does not destroy fungus unless a very large dose is used; its action in treating ringworm of the scalp depends upon the epilatory effect and not upon any direct influence on the fungus.

F. F. HELLIER, M.D., F.R.C.P.

PRACTICAL NOTES

The Treatment of Obesity

As a result of their experience in the treatment of 299 cases of obesity, D. Adlersberg and M. E. Mayer (*Journal of Clinical Endocrinology*, March 1949, 9, 275) are of the opinion that in the majority of cases as satisfactory results are obtained with a low calorie diet (1200 cal.) as with a low calorie diet combined with thyroid or with amphetamine. In assessing the value of any form of treatment of obesity emphasis is laid upon the necessity for differentiating between the short-term effect and the long-term results. Irrespective of the form of treatment, best results were obtained in the first one or two months of treatment. During this period dietetic control alone was better than diet plus thyroid, but not quite as good as diet plus amphetamine. On the other hand, the initial effect of amphetamine gradually wore off, and to maintain a fall in weight larger doses had to be given. This induced unpleasant side-effects in some patients, such as dry mouth, halitosis and addiction. In two instances amphetamine poisoning occurred. The long-term results with diet alone compared favourably with those obtained with diet plus amphetamine. It is concluded that "amphetamine preparations should not be dispensed and refilled without a physician's prescription. These drugs should not be used routinely in the treatment of obesity. Patients to whom they are administered should be closely observed".

Decamethonium Iodide in Anaesthesia

A REPORT on preliminary trials with decamethonium iodide (bistrimethylammonium decane diiodide) in anaesthesia as a substitute for *d*-tubocurarine is given by G. Organe (*Lancet*, May 7, 1949, i, 773). In light surgical anaesthesia a single intravenous injection of 3 mg. decamethonium iodide produced good muscular relaxation without undue depression of respiration; thus, it is stated that this dose may be taken as approximately equivalent to 15 mg. of *d*-tubocurarine chloride. Apnoea, lasting for ten to twenty minutes, followed an injection of 4-5 mg. After the initial administration, further injections are made at intervals of ten to forty minutes, dosage depending upon the preceding interval, e.g., after forty minutes a further 3 mg. will probably be necessary. The total dosage employed was 1.5 to 10 mg. The action of the drug on the respiratory system causes thoracic and abdominal breathing to fail and recover together; there is no direct effect on the cardiovascular system. It is stated that "pentamethonium iodide, in a dose ten times that of decame-

thonium iodide, has proved an effective antidote. It produces a powerful block of autonomic ganglia in animals. . . . We have found its use unnecessary in anaesthetic practice". This view on the antidotal value of pentamethonium iodide is not supported by A. J. H. Hewer *et al.* (*Ibid.*, May 14, p. 817), who state that owing to its autonomic blocking effect, which might be a contributory factor in operative shock, "the antagonist pentamethonium iodide has no useful place in anaesthetic practice". On the value of decamethonium iodide as a muscle relaxant in surgical anaesthesia these authors, who used a somewhat different dosage—(1) initial dose 3-5 mg. followed by 1-3 mg. as required; (2) initial dose 1 mg. per 15 kg. body weight, followed by approximately one-half to one-third of this amount; total dosage 3-15 mg.—state: "It is a satisfactory relaxing agent with a wide margin of safety, provided adequate pulmonary ventilation is maintained. Its effect is transient, but this is unimportant since repeated doses have no cumulative effects. There are no significant side-effects". According to G. Organe (*Ibid.*, May 7, p. 773) there were some postoperative reactions: vomiting, 25 per cent.; retention of urine, 9 per cent.; and lobar collapse in five patients. There was a reduced incidence of abdominal distension. The value of decamethonium iodide in conjunction with thiopentone in patients undergoing electrically produced convulsions is recorded by D. L. Davies and Aubrey Lewis (*Ibid.*, May 7, p. 775), who state that it "proved safe, effective for this purpose, and without disagreeable side-effects"; and J. A. Hobson and F. Prescott (*Ibid.*, May 14, p. 819): "Decamethonium iodide has all the advantages of other curarising drugs; the traumatic complications of convulsive therapy are avoided; there is no serious rise in blood pressure; and it enables convulsion therapy to be given to certain patients in whom otherwise convulsions would be contraindicated. Decamethonium iodide is to be preferred to *d*-tubocurarine for this purpose, as it has no tendency to produce histamine-like reactions, and as the curarisation passes off more rapidly".

Perforated Adhesive Tape for Umbilical Hernia

A REPORT of the results obtained in a series of 100 infants with acquired umbilical hernia, 50 of whom were treated by application of adhesive tape with multiple perforations, and 50 as controls with standard non-perforated adhesive tape, is given by R. Cohen (*American Journal of Diseases of Children*, July 1948, 76, 44). The

tape employed was 2 inches (5.08 cm.) in width, with multiple perforations $\frac{1}{8}$ of an inch (0.32 cm.) in diameter, spaced at $\frac{1}{4}$ -inch (1.27 cm.) intervals. It was noted that the perforated adhesive tape allowed more surface ventilation and twenty times more light to pass through; also the perforated tape was lighter than the unperforated, and a lesser quantity was used. On removal of the perforated tape after seven to ten days the following points were noted: (a) Rows of dotted normal skin, $\frac{1}{8}$ in diameter were present which were of assistance in re-taping; (b) there was 50 per cent. less irritation of the skin with the perforated tape; (c) no bleeding occurred, nor were there any pustulations or vesiculations present; (d) infants allergic to adhesive tape showed fewer areas of irritation with the perforated tape; (e) the results in the control group treated with non-perforated tape were not as good as those treated with the perforated tape; (f) on removal of the perforated tape it was found that the area could be cleaned immediately and re-taped without loss of time or setbacks. It is calculated that there was about 50 per cent. improvement with the use of multiple perforated adhesive tape, as shown by fewer dermatological lesions, compared with the use of standard non-perforated adhesive tape.

Coronary Vasodilator Action of Khellin

KHELLIN, a crystalline substance extracted and isolated from the seeds of *Amni Visnaga*, a plant which grows wild in the Eastern Mediterranean countries and known in Arabic as "khella", decoctions from the seeds of which have been used as antispasmodics since ancient times, has been given clinical trial in 300 patients with coronary artery disease by G. V. Anrep, M. R. Kenawy, and G. S. Barsoum (*American Heart Journal*, April, 1949, 37, 531). The cases were divided into two groups: 250 patients with angina of effort or decubitus, and 50 patients with coronary thrombosis, with or without anginal attacks during the period of absolute recumbency. In order to eliminate any possible psychic element in the action of the drug, placebos were given in the form of injections or tablets containing no khellin, or else the dose of khellin was suddenly reduced without the patient's knowledge. Khellin was administered in three ways: (a) as purified liquid extract containing 50 mg. of the active principle per ml., the dose being 1 to 2 ml. diluted in water, taken with meals; (b) as tablets containing 50 mg. khellin, one to two tablets after meals; (c) intramuscular injections in strength of 50 mg. per ml., 2 ml. being injected once or twice daily, and during anginal attacks. The minimal effective daily dosage of khellin daily was calculated as 2 mg. per kg. body weight. In the 250

patients with angina pectoris, distinct improvement was noted in 140 cases, moderate improvement in 85 cases, and no effect in 25 cases. Oral therapy was used in most cases, except when response was delayed or the case was severe. For the treatment of individual attacks, liquid extract was given during the attack, relief being obtained in 70 per cent. of cases. In prolonged attacks intramuscular injections of 100 mg brought relief in a few minutes. It is stated that "on the whole, the relief obtained was slower than after trinitrin tablets". Of the 50 patient with acute coronary thrombosis, 12 died during the first or second week of treatment; the remainder recovered. Khellin, in conjunction with morphine, was given in single doses of 100 mg continued daily for a period varying from six weeks to three months. Control and relief of the anginal attacks were obtained. Among the advantages claimed for khellin are: (a) no toxic effects; (b) no habituation to the drug; (c) prolonged action.

Penicillin in Human Milk

THE concentration of penicillin in human milk following the intramuscular administration of 200,000 to 600,000 units of crystalline potassium penicillin G in thirteen women was studied by R. Rozansky and A. Brzezinski (*Journal of Laboratory and Clinical Medicine*, April 1949, 34, 497). Significant concentrations of penicillin were found in the milk in twelve cases. At the end of one hour the concentration of penicillin ranged from <0.03 to 0.36 unit per ml. It continued to rise until the fourth hour after the injection, when the concentration ranged from <0.03 to 0.96 unit per ml. The concentration began to fall after six hours, but in the three cases in which the concentration was measured nine hours after the injection the figures were 0.03, 0.12, and 0.16 unit per ml. One patient, following an initial dose of 400,000 units of penicillin, was given 30,000 units intramuscularly every three hours, and in her the concentration of penicillin in the milk remained at 0.48 unit per ml. for six hours. The levels of penicillin in the serum were also measured, and it was found that at the end of two hours the concentration in the milk was 10 to 15 per cent of that in the serum, whilst subsequently the milk concentration remained constant or rose and the serum level fell.

Glycine in the Treatment of Peripheral Vascular Disease

ON the basis of experimental evidence indicating that glycine increases peripheral blood flow J. R. Gustafson and his colleagues (*Surgery*, April 1949, 25, 539) studied the effect of this

amino-acid in 35 patients with arteriosclerotic peripheral vascular disease, 13 with thromboangiitis obliterans, seven with Raynaud's disease, and five with "miscellaneous vascular diseases with associated vasospasm". The glycine was given orally in doses of 20 g. twice or thrice daily. To disguise its sweet taste, it was taken with black coffee, lemon juice, or milk flavoured with bitter chocolate. There were no side-reactions from its use. Of the 35 patients with arteriosclerotic vascular disease, the average age of this group being sixty, 13 obtained complete or marked relief, whilst eight obtained no relief at all. Of the 13 patients with thromboangiitis obliterans, eight were treated initially with tetraethylammonium salts and then given maintenance doses of glycine, and seven of these had remained asymptomatic for four to thirteen months. Five were treated with glycine alone and they all showed sufficient improvement to be able to return to work. Of the seven patients with Raynaud's disease, only one showed complete relief with glycine, whilst five showed some improvement. Two of the five patients in the miscellaneous vasospastic group showed "a dramatic response". It is concluded that glycine is "a definite adjunct to the conservative treatment of peripheral vascular insufficiency" and that "it is inexpensive, can be taken orally, is completely safe and, theoretically, could produce virtually constant vasodilatation twenty-four hours a day".

Rutin in Toxæmias of Pregnancy

"RECENT studies on hypertensive patients have shown that approximately 18 per cent. of them have an abnormal capillary fragility . . . hypertension of varying degrees is found in over 8 per cent. of . . . pregnant patients". Rutin, a rhamno-glucoside of quercetin, is a flavon derivative with a formula similar to hesperidin; the latter has been shown to have a beneficial action on abnormal capillary fragility. Rutin is stated by W. J. Dieckmann, Z. Akbasli and G. T. Aragon (*American Journal of Obstetrics and Gynecology*, April, 1949, 57, 711) to be preferable to hesperidin because "it is more effective in smaller doses and so far no toxic symptom has been noted in laboratory animals or in patients". Following the estimation of capillary fragility, using both positive and negative pressure tests, in 164 cases of toxæmia of pregnancy, in 33 per cent. of which increased capillary fragility was found, 13 pregnant women with abnormal capillary fragility were treated with rutin. The initial dosage was 20 mg. t.d.s., the fragility being determined at three weeks. If no improvement was found after the first three weeks the dose was doubled. After return of the capillary fragility index to normal

levels, a dosage of 20 mg. t.d.s. was maintained until delivery. It is stated that in pregnant hypertensive patients with abnormal capillary fragility, 60 mg. of rutin daily is insufficient; in almost every case the dose had to be increased to 120 mg. daily. No toxic symptoms were observed. A few patients received ascorbic acid in conjunction with rutin, although there was no evidence of any signs of vitamin C deficiency in toxæmias of pregnancy. Twelve of the thirteen patients treated gave fair to good results; in the remaining case the condition worsened in spite of rutin therapy.

In one case, that of a forty-two year old woman in her eighth pregnancy, the blood pressure ranged from 148/84 to 100/100, and at 27 weeks' gestation the capillary fragility was markedly abnormal. She was given rutin, 20 mg. t.d.s., increased two weeks later to 40 mg. t.d.s. At 31 weeks' gestation capillary resistance was normal and the rutin was reduced to 60 mg. daily. Ten days later both Göthlin and Hecht-Dalldorf tests were normal, and at 34 weeks the patient was delivered by Cæsarean section of a 2.145 kg. male infant. Rutin was stopped, and at six to ten weeks postpartum capillary fragility was abnormal with both tests.

Calciferol in the Treatment of Psoriasis

USING a dosage of 25,000 I.U. daily in children, and 50,000 I.U., at times increased to 100,000 I.U., daily in adults, a series of 31 patients with psoriasis, mostly women and children, were treated with calciferol. The results are recorded by Theresa Kindler (*Proceedings of the Royal Society of Medicine*, March 1949, 42, 140). In 12 cases (chronic and generalized) the treatment resulted in almost complete disappearance of the eruption; in some cases there was a mild relapse within four weeks to three months which responded well to local treatment with mild ointment, with or without calciferol. Improvement, but with slower progress, was noted in 7 of the remaining cases; in 6 there was no response to treatment; in 3 cases the drug had to be stopped because of intolerance, and 2 patients defaulted.

Penicillin-Vitamin C in Infective Endocarditis

A COMBINED intravenous course of 360,000 units daily of penicillin with vitamin C (5000 I.U. every 12 hours in the same syringe as the penicillin) was given by L. Gibelli and L. Garelo (*Informatore Medico*, 1948, 11, 255) to a 24-year-old woman with infective endocarditis. Complete recovery resulted within twenty-one days. Two million units of penicillin by itself had previously been ineffective. Gibelli had already obtained 60 per cent. cures by this method (*Folia Cardiologica*, 1947, 6, 405). *In vitro* experiments to test these clinical results were inconclusive, but the authors believe that the addition of vitamin C does not alter the action of penicillin.

REVIEWS OF BOOKS

Essentials of Orthopædics. By PHILIP WILES, M.S., F.R.C.S., F.A.C.S. London: J. & A. Churchill Ltd., 1949. Pp. xv and 486. Figures 365 and 7 plates in colour. Price 42s.

THIS book is designed primarily to meet the needs of the general practitioner, the undergraduate, and the postgraduate who is beginning his surgical training. It attains its object. Very properly it opens with a chapter on the important subject of postural defects. Although there may be criticism of details, the principles enunciated will be generally accepted. This chapter in particular should be read by those who are responsible for the care of children and adolescents. Views about the cause and treatment of sciatica have undergone radical changes in the last few years. The author deals with this subject fully and clearly, but perhaps tends to minimize the good effects of rest. The book is comprehensive, is written in an easy and interesting style, and successfully fills a gap in the literature of orthopædic surgery.

Some Common Psychosomatic Manifestations. By J. BARRIE MURRAY, M.D., M.R.C.P. London: Oxford University Press, 1949. Pp. xii and 101. Price 7s. 6d.

THE title of this book is misleading, and perhaps a better indication of the author's approach to his subject would be "The Effort Syndrome and other Psychosomatic Manifestations". The author is to be congratulated on his clear presentation of the salient but varied features of the effort syndrome, and particularly on avoiding psychological jargon. As a result, this little book has an essentially clinical approach and makes pleasant reading. The final chapter on treatment offers some sound advice on the general principles that must be observed in dealing with psychosomatic disorders.

Current Therapy 1949. EDITED BY HOWARD F. CONN, M.D. London and Philadelphia: W. B. Saunders Company, 1949. Pp. xxxii and 672. Price 50s.

BOTH the publishers and Editors of this book are to be congratulated on producing an authoritative and up-to-date account of modern therapy. The Editors have wisely avoided "reviews of recent literature" and accounts of new drugs or methods of therapy that have not yet been subjected to controlled clinical trial and critical evaluation. Instead, they have presented the latest standard methods of treatment in current use, and where opinions differ over the therapy of any specific disease or group of

diseases alternative methods of treatment are presented. The book is conveniently compiled in sections which facilitate easy reference. It is particularly pleasing to see that treatment of the common cold has not been omitted (a fact which authors and editors of other books on medical treatment would do well to note). Subjects which are particularly well presented include essential hypertension, allergy, hyperthyroidism, diabetes and ulcerative colitis. The book is one which will prove valuable not only to practitioners but also to consultants. There is a convenient and detailed index for quick reference.

Modern Practice in Psychological Medicine.

EDITED BY J. R. REES, M.D. London: Butterworth & Co. (Publishers) Ltd., 1949. Pp. xii and 475 + index. Price 50s.

TWENTY-NINE experts have contributed to this book, which contains a fund of information on many aspects of psychiatry. The origins of mental disorder, its physiology and psychology, its care and cure and its legal bearings in various countries are described. It is a book for the psychiatrist rather than the general practitioner. A number of the contributions are somewhat technical, and they present such diverse medical and psychological points of view as perhaps to confuse the more general reader. To those, however, who possess some basic psychiatric knowledge it will be stimulating and instructive, and can be thoroughly recommended.

Marriage Counselling. By DAVID R. MACE, B.Sc., Ph.D. With a foreword by the Rt. Hon. HENRY WILLINK, M.C., K.C. London: J. and A. Churchill Ltd., 1948. Pp. xi and 167. Price 8s.

THIS work is the first full account of the remedial work of the Marriage Guidance Council. The chief doubts which beset the medical reader are perhaps the following: The author admits that many unsuitable persons are anxious to offer themselves as counsellors, and one can only hope that those actually chosen are in fact suitable in the first place, and are also capable of learning by experience and by discussion. Secondly, Dr. Mace (p. 81) writes: "Psychological investigation and treatment, moreover, are very time consuming". Psychiatrists are to be called in only if the individual's speech or conduct appears to be "irrational". It is therefore as well (he thinks) if the guidance of the psychological consultants is to be retained, to make sparing use of their services. Some people however, may think that the ideal procedure

would be for the psychiatrist to be called in at the beginning, when the relative physical and psychological factors could be correctly assessed. Thirdly, although medical men are said to be consulted in cases of physical disability, the author evidently considers (p. 126) that impotence is seldom a matter for the doctor. Nevertheless, it would seem wise for the medical profession to work closely with this new organization, which has almost certainly come to stay and which may do much to combat one of the greatest social evils of our time.

Penicillin and Other Antibiotics. By G. W. S. ANDREWS, M.B., B.S., and J. MILLER, B.Sc. London: Todd Publishing Group Ltd., 1949. Pp. vi and 154. Illustrated. Price 7s. 6d.

IN spite of the appalling dustcover, which is more reminiscent of the Marie Corelli type of publication so beloved by the less intelligent than of a scientific work, this is a book well worth reading. The authors, who are members of the staff of the Wright-Fleming Institute of Microbiology, St. Mary's Hospital, have attempted, and with considerable success, to present a short scientific survey of antibiotics. This is a subject which has grown so tremendously during the last ten years that it has become almost a specialized branch of science in itself. The ordinary clinician is therefore rather lost, and this book will provide him with a useful survey of the more scientific aspects of the problem, couched in relatively simple terms. Naturally, pride of place is given to penicillin and streptomycin, but tyrothricin is also included. This is primarily a book for medical and pharmaceutical students, and as such can safely be recommended.

Evolution of the Forebrain. By G. W. H. SCHEPERS, M.D., D.Sc. Capetown: Maskew Miller Ltd., 1948. Pp. 212. Figures 250. Price 50s.

THIS book is a detailed study of the reptilian brain, in particular the forebrain of *Testudo geometrica*. The author has previously described the external morphology of this brain, and the present work is concerned with the evolution of cell formations and the cyto-architectonics of the telencephalon. Essentially a textbook for the anthropomorphic specialist, it ranks with the work of Elliot Smith and Arienso Kappers. There is a stimulating introductory chapter on the general evolution of the forebrain and its bearing on the interpretation of cerebral physiology and psychology. It is fitting that a work of this nature should emerge from Johannesburg which has already contributed to the

elucidation of controversial evolutionary problems, and that it should be dedicated to Professor Raymond Dart, one of our foremost anthropologists.

NEW EDITIONS

EXTENSIVE revision has been undertaken in the preparation of the second edition of *Recent Advances in Oto-Laryngology*, by R. Scott Stevenson, M.D., CH.B., F.R.C.S.E.O. (J. & A. Churchill Ltd., 24s.) and three new chapters have been added, dealing respectively with chemotherapy and antibiotics, hearing aids, and aviation oto-laryngology. In the chapter on otosclerosis there is a detailed account of the fenestration operation; in the chapter on Ménière's disease the technique of sympathectomy is discussed; these are among the many additions to this practical presentation of oto-laryngology.

Cystography and Urography, by J. B. Macalpine, D.Sc., F.R.C.S., in its third edition (John Wright & Sons Ltd., 63s.) contains among new additions a chapter on the pathology of urinary tuberculosis, and a section on the punch operation for prostatic hypertrophy. As this work has been unobtainable for a number of years owing to the destruction during the war of the previous edition and the material for a reprint, the new edition contains a wealth of new material. It is beautifully produced.

SECTIONS on penicillin, the anticoagulants and other advances in chemotherapy are among the additions to *Handbook of Surgery*, by Eric C. Mekie, M.B., CH.B., F.R.C.S.ED., F.I.C.S., and Ian Mackenzie, M.B.E., M.B., CH.B., F.R.C.S.ED., in its second edition (E. & S. Livingstone Ltd., 20s.), and there is a section on the surgical treatment of "blue babies". This work is intended chiefly for those preparing for the final examination in surgery, and the authors' plan of setting out the clinical features, methods of examination, and then treatment will be appreciated for its conciseness.

Psycho-Analysis: A Handbook for Medical Practitioners and Students of Comparative Psychology, by Edward Glover, M.D., in its second edition (Staples Press Ltd., 15s.) has been revised and expanded. The work terminates with a useful glossary of terms used in psychiatry, and a list of books recommended for study.

THE fourth edition of *Medical Photography*, by T. A. Longmore, F.S.R. (Focal Press, 50s.) has been considerably expanded and is now a very thorough reference book dealing with both theoretical and practical aspects of the subject.

NOTES AND PREPARATIONS

NEW PREPARATIONS

GELATIN SPONGE A & H has been prepared for use as a hæmostatic in cases of bleeding which cannot be dealt with by ligature. This dry sterile sponge or foam is issued in convenient sized pieces, each piece packed in a glass tube for issue as a separate sterile unit; available in boxes of 6. **PENICILLIN STYPTIC POWDER** (20,000 units of penicillin calcium salt per gramme) is issued in tubes of 2 g., in special aluminium tube containers designed to facilitate application to minor wounds and dental sockets following extraction. (Allen & Hanburys Ltd., Bethnal Green, London, E.2.)

LACHESINE (benzilyloxyethyl dimethylammonium chloride) is a new mydriatic drug with a strength lying between that of atropine and hyoscine. Its use is indicated in cases of allergy to atropine and when treatment must be continued over a long period. Issued in vials of 1, 5, 10, 15 and 25 g., and in bottles of 15 g. (British Chemicals & Biologicals Ltd., 43 Regent Street, Loughborough.)

LINGUETS OF PERCORTEN (deoxycortone acetate B.P.), each containing 1 mg. of cortical hormone in a specially prepared tablet for sublingual absorption, are stated to be suitable for maintenance therapy or to supplement other methods of administration of the hormone in the treatment of Addison's disease and conditions of impaired adrenal function. (Ciba Laboratories Ltd., Horsham, Sussex.)

'**NEO-SELAROM**' is a salt substitute containing potassium and ammonium chloride, potassium and calcium formate, and magnesium citrate. Its use is indicated in conjunction with sodium-restricted diets in the treatment of cardiac and renal diseases. Available in bottles of 2 and 8 ounces. (Bayer Products Ltd., Africa House, Kingsway, W.C.2.)

ROSE-HIP L.B.W. (rose-hip syrup 25 per cent., pure orange concentrate 50 per cent., barley water 25 per cent.) contains no saccharin, and the vitamin C content is 20 mg. per fluid ounce. It is a palatable drink, and should prove popular with children and invalids. The retail price is 4s. 6d. per 26-ounce bottle. A free sample is available. (L.B.W. Ltd., 46 Grainger Street, Newcastle-on-Tyne 1.)

MEDICAL FILM

A SHORT film entitled "Growing Girls", in which the process of menstruation is explained, has been prepared by Southalls (Birmingham) Ltd., for exhibition in schools. (Sound Services Ltd., 269 Kingston Road, Merton Park, S.W.19.)

NAPT LOCUM REGISTER

THE National Association for the Prevention of Tuberculosis has set up a Locum Register for doctors seeking temporary positions in clinics and sanatoria. Practitioners desiring work of this kind are asked to send necessary details with qualifications and, if possible, their telephone number, to the NAPT Locum Register, Tavistock House North, London, W.C.1.

OFFICIAL NOTICES

Ambulance Services (E.C.L. 193) states the Local Health Authorities' ambulance service are available for special transport free of charge but such Authorities are not empowered to reimburse under the National Health Service the cost of arrangements privately made. D.L. 98524/1 deals with the arrangements that can be made by Local Health Authorities with the Railway Executive for reservation of a compartment for patients, including stretcher cases making long journeys.

Rye Flour for Patients Allergic to Wheat (P.N. 5426a).—Such patients need no longer produce a medical certificate to obtain supplies of rye flour. In the event of difficulties advice should be sought from the Local Food Office.

Food Poisoning (Memo. 188/Med.) gives details of the steps to be taken in England and Wales by Medical Officers of Health in the investigation of food poisoning. (H.M. Stationery Office price 3d.)

PUBLICATIONS

National Register of Chiropractors, 1949.—The seventh edition is available free of charge on application to the Registrar of the Board of Medical Auxiliaries, Tavistock House North, Tavistock Square, London, W.C.1.

Home Ambulance Service, 1948, gives details of the Ambulance Services throughout the country. The Service is not included in the National Health Scheme. (Home Service Ambulance Department, British Red Cross Society, 1 Grosvenor Crescent, London, S.W.1.)

The Physique of Adult Males (Med. Res. Council Mem. No. 20), by W. J. Martin. (H.M. Stationery Office, price 1s. 3d.)

Estimation of Sulphonamides, in its third edition (May & Baker Ltd., Dagenham, Essex.)

Eli Lilly & Co. Ltd., Basingstoke. The new edition of this firm's Price List is now available.

Vade Mecum of Medical Products, 1949, is available on application to Evans Medical Supplies Ltd., Speke, Liverpool 19.

The contents of the August issue, which will contain a symposium on "Gynaecology", will be found on page 10 at the end of the advertisement section.

THE PRACTITIONER

No. 974

AUGUST 1949

Volume 163

THE PRESENT STATUS OF TREATMENT OF CANCER OF THE UTERINE CERVIX AND BODY

By JAMES YOUNG, D.S.O., M.D., F.R.C.S., F.R.C.O.G.

*Professor of Obstetrics and Gynaecology, University of London; Director,
Department of Obstetrics and Gynaecology, Postgraduate Medical School,
London.*

THREE recent discoveries relating to uterine cancer have an important bearing on treatment and prognosis:—

(1) There is good evidence that cancer of the cervix often occurs as long as ten years before there is clinical evidence of its presence. For the greater part of this time it is "non-invasive".

(2) The vaginal smear method, which depends upon the vaginal fluids containing samples of all the desquamated epithelial cells from the body and cervix of the uterus, detects malignancy with a considerable accuracy and at an earlier stage than has previously been possible.

(3) There is evidence that, by appropriate methods, we can decide which cases are more suited for radiotherapy and which for surgery.

NON-INVASIVE CANCER OF THE UTERUS

It has for long been recognized, e.g., in the breast and the skin, that the invasive type of growth which is clinically familiar is often preceded for a period of years by changes in the nuclei and the cytoplasm of the epithelial cells similar to those found in cancer, but which are not associated with any breach of the basement membranes. This condition is exemplified in Bowen's cancer of the skin and in the intra-epithelial cancers of mucous membrane. Within recent years many records of this condition in the cervix have been published. It has been found in routine examination of tissue removed for some other reason, e.g., during cervical repair or during a prolapse operation, and in which there was no clinical evidence of cancer. Galvin and Te Linde (1949) found in such material 75 examples of intra-epithelial cancer. The outstanding fact, which they and other authors have stressed, is that although in general there is an absence of any symptoms or local changes pointing to invasive carcinoma, this can be found by careful

examination of the cervix in a considerable proportion of cases. In Galvin and Te Linde's 75 cases a histological search revealed invasive cancer elsewhere in the cervix in 55 cases. In the remaining 20 cases no invasive lesion was found. The next important finding is that non-invasive cancer followed-up over a period of years has been found to become invasive: after 9 years (Stevenson and Scipiades, 1938); after 4 years and 9 months (Pund *et al.*, 1948); after 7 years (Taylor and Guyer, 1946). These sample data from the large amount of evidence now available prove that intra-epithelial cancer often coexists with a true, although still asymptomatic, cancer, or that it may progress over a considerable number of years into a true invasive growth.

There is as yet no accurate knowledge of the frequency with which a non-invasive growth develops into an invasive growth, and there are gynaecologists who maintain that the proper management of the case consists of periodic biopsy and the institution of active therapy only when invasion is established. During the discussion on the paper of Galvin and Te Linde at the American Gynecological Society last year, Scheffey (1949) stated that he had six patients in whom the original cervical biopsy had revealed intra-epithelial carcinoma six years before, and who had remained well and in whom subsequent biopsy had failed to reveal any lesion. Scheffey rightly pointed out, however, that this might merely imply that the disease in its early stage had been removed completely at the initial biopsy. On these questions it is still not possible to give a definite opinion. ?

It is probably of considerable significance that, whilst the average age at which clinically the first symptoms of cancer appear is about forty-eight years, the average age for the finding of non-invasive cancer is thirty-six to thirty-seven years (Galvin and Te Linde, 1949; Pund and Auerbach, 1946).

THE VAGINAL SMEAR METHOD

This method, first fully described by Papanicolaou and Traut in 1941, has made it possible in many cases to recognize non-invasive and invasive cancer before symptoms or local clinical signs have appeared. It consists of the removal by means of a pipette of the fluid secretion of the vagina or the endocervix. From this a smear is made and stained. Cancer cells are recognized by their characteristic nuclear and cytoplasmic appearances. Since the publication of Papanicolaou and Traut's monograph a large literature on the subject has appeared. Whilst there are differences of opinion in regard to the technique, the methods of application of the procedure and the interpretation of the results, there is a consensus of opinion in regard to its great value. The method is now in routine employment in many gynaecological clinics, especially in America, and there is a large mass of evidence regarding its reliability.

Out of a total of 1,045 women so examined by Isbell *et al.* (1947), there were 58 proved cases of cancer of the uterus. In 40 cases of carcinoma of the cervix the smear was positive in 39, and in 18 cases of cancer of the body it was positive in 15 and negative in three. Fremont-Smith *et al.* (1947), examined 5,621 women, of whom 492 had proved uterine cancer; in 113 cases of endometrial cancer the smear

was correct in 83, or 73.5 per cent., whilst it was correct in 317 out of 354 cases of cervical cancer, or 89.5 per cent. These authors point out, however, that the smear has its special value in the detection of symptomless, non-invasive cancer and they record 30 cases in which the smear was positive in 23, whilst in 27 of the same patients the biopsy was correct in only 13. They emphasize the simplicity of the method and that, by revealing the presence of suspicious cells, it directs attention to the need for a careful study by means of biopsy and, if need be, for continuing and strict observation.

During the ten months that the method has been in use at the Postgraduate Medical School in London we have detected two early invasive cancers of the cervix and two cases of non-invasive cervical cancer. These cases were discovered at biopsy, dictated by the finding of suspicious cells in the smears. In none of the cases was there a lesion recognizable by the ordinary methods of examination, and in three cases there were no suspicious symptoms.

The smear method depends for its accuracy upon the skill of the observer, and this can be acquired only after a considerable number of months' training in the assessment of the varying cellular elements in the discharge, and, more especially, upon a sound appreciation of the cytological criteria of malignancy. It demands specially trained personnel, who are made available for a service which is somewhat time-consuming. Whilst its greatest use is naturally in a gynaecological department in the "screening" of women reaching the cancer age, i.e., over thirty, it has in some quarters in America been extended more universally, and has been used as part of the periodic medical overhaul which has become popular in that country.

In this country, where this system is less in use, the smear method has its chief application in the gynaecological clinic and ward. Here, in women who have pelvic complaints, more especially if these are associated with morbid discharges, there is a selected field in which the incidence of carcinoma is naturally higher than in the outside population. It has been estimated by two independent workers in the United States that the incidence of cervical carcinoma in the female population at large is 1 in 1,500 women over the age of thirty-five, and that to discover one such case would require about 500 hours of microscopy. This gives point to the argument against the employment of the procedure as a general public health measure. At the same time, there is sound reason for extending the availability of a method of such potential value in the early detection of cancer beyond the confines of the large hospital department, which alone will generally be able to provide the skilled personnel required. With this in view, a service centred in the hospital but open to outside practitioners has been successfully operating in some Transatlantic clinics.

I have already indicated that a smear diagnosis alone is not sufficient to justify active therapy. Such a diagnosis must be confirmed by biopsy before such steps are taken. Even when the biopsy reveals intra-epithelial or non-invasive carcinoma, it is as yet not clear whether or not more active measures than a continuing and strict scrutiny by smear and biopsy are justified. In view, however, of analogy from other regions, e.g., the skin, in which this lesion is prone to invasion sooner or later, a good case for the institution of active measures could be adduced, especially if the patient were in late

examination of the cervix in a considerable proportion of cases. In Galvin and Te Linde's 75 cases a histological search revealed invasive cancer elsewhere in the cervix in 55 cases. In the remaining 20 cases no invasive lesion was found. The next important finding is that non-invasive cancer followed-up over a period of years has been found to become invasive: after 9 years (Stevenson and Scipiades, 1938); after 4 years and 9 months (Pund *et al.*, 1948); after 7 years (Taylor and Guyer, 1946). These sample data from the large amount of evidence now available prove that intra-epithelial cancer often coexists with a true, although still asymptomatic, cancer, or that it may progress over a considerable number of years into a true invasive growth.

There is as yet no accurate knowledge of the frequency with which a non-invasive growth develops into an invasive growth, and there are gynaecologists who maintain that the proper management of the case consists of periodic biopsy and the institution of active therapy only when invasion is established. During the discussion on the paper of Galvin and Te Linde at the American Gynecological Society last year, Scheffey (1949) stated that he had six patients in whom the original cervical biopsy had revealed intra-epithelial carcinoma six years before, and who had remained well and in whom subsequent biopsy had failed to reveal any lesion. Scheffey rightly pointed out, however, that this might merely imply that the disease in its early stage had been removed completely at the initial biopsy. On these questions it is still not possible to give a definite opinion. ?

It is probably of considerable significance that, whilst the average age at which clinically the first symptoms of cancer appear is about forty-eight years, the average age for the finding of non-invasive cancer is thirty-six to thirty-seven years (Galvin and Te Linde, 1949; Pund and Auerbach, 1946).

THE VAGINAL SMEAR METHOD

This method, first fully described by Papanicolaou and Traut in 1941, has made it possible in many cases to recognize non-invasive and invasive cancer before symptoms or local clinical signs have appeared. It consists of the removal by means of a pipette of the fluid secretion of the vagina or the endocervix. From this a smear is made and stained. Cancer cells are recognized by their characteristic nuclear and cytoplasmic appearances. Since the publication of Papanicolaou and Traut's monograph a large literature on the subject has appeared. Whilst there are differences of opinion in regard to the technique, the methods of application of the procedure and the interpretation of the results, there is a consensus of opinion in regard to its great value. The method is now in routine employment in many gynaecological clinics, especially in America, and there is a large mass of evidence regarding its reliability.

Out of a total of 1,045 women so examined by Isbell *et al.* (1947), there were 58 proved cases of cancer of the uterus. In 40 cases of carcinoma of the cervix the smear was positive in 39, and in 18 cases of cancer of the body it was positive in 15 and negative in three. Fremont-Smith *et al.* (1947), examined 5,621 women, of whom 492 had proved uterine cancer; in 113 cases of endometrial cancer the smear

cases will be in the advanced stage (stage IV), but even here, again according to the Radiumhemmet figures, there is a five-year survival rate of 7 per cent. Therefore to obtain a fair assessment of the two competing methods, a minimum percentage chance of survival of 2.6 (i.e. 7 per cent. of 37) must be added to Bonney's results. This confirms the conclusion that in general the salvage achieved by surgery as the primary choice, with radiotherapy for the advanced cases, is very similar to that obtained with radiotherapy alone.

It is thus apparent that the common claim that radiotherapy should be the method of choice in cervical cancer requires some qualification. Nevertheless, as technique in both the surgical and radiotherapeutic fields is still progressing, there is reason for a suspension of judgment while each procedure is given a full opportunity to realize its full potentialities.

In the field of surgery within recent years there have been various attempts to extend the range of the operative removal for cervical cancer beyond the limits previously set for the Wertheim procedure. Modern surgery has at its command measures for protecting life, such as perfected methods for blood transfusion and chemotherapy, which were denied to the operator even a decade ago. These permit of a wide extension of the legitimate field for the scalpel.

Brunschwig (1948) has recently published a record in which, out of 81 patients seen, a radical procedure was carried out in 67 or 82.7 per cent. This consisted in 37 cases of a complete removal of the uterus and adnexæ, the entire broad ligaments and paravaginal tissues, the pelvic lymph nodes, lymph channels and areolar tissues about the common iliac, external iliac and hypogastric vessels, the lymph nodes and areolar tissue in the obturator fossæ, the areolar tissues on the posterior and lateral surfaces of the bladder and, finally, practically the entire visceral and parietal peritoneum of the pelvis with its subjacent areolar tissues. In a further 24 cases the operation included, in addition, excision of part or all of the bladder and the other pelvic viscera, with in some instances ureteral implantation into the colon and colostomy. In six stage I cases the radical vaginal extirpation according to Schauta was performed. The immediate mortality in this series of 67 radical operations had the low figure of 4, or 5.9 per cent.

In the field of radiotherapy, also, considerable progress has taken place within the last decade and this is reflected in better attainable results. This has followed from a widening recognition of the necessity for the close collaboration of the gynaecologist, the radiotherapist and the physicist. The function of the gynaecologist is to determine the extent and localization of the disease, to deal with any associated complications, such as sepsis, and to supervise the clinical follow-up; whilst the radiotherapist requires the help of the physicist in ensuring that the irradiation is so planned as to achieve as complete coverage of the field as is possible. The high skill required at each level of this triple team implies of necessity that the treatment can be efficiently carried out only in centres specially organized for the purpose.

In the meantime, whilst surgery and radiotherapy are engaged each in establishing its claims, it is clear that any practicable method of foretelling with any individual growth whether or not it is likely to respond to radiation

reproductive life. We are naturally faced with the dilemma that whilst treatment at this very early stage gives a favourable prognosis (even in the relatively advanced clinical stage I, the five-year survival free from disease is about 70 to 80 per cent.), delay will necessarily depress the prognosis should the case eventually prove to be true carcinoma.

Some variations of the smear method have been described. Thus Ayre (1948) uses a wooden spatula to remove the cervical epithelium, whilst Novak (1948) employs a scalpel or a spoon with cutting edges to remove the entire area of mucous membrane at the junction of the vaginal and endocervix. These procedures tend, however, to partake of the features of a biopsy and to lose to this extent the simplicity which is the cardinal feature of the smear method. For the fuller investigation that becomes necessary in the presence of a positive or suspicious smear, however, they have their place, as in the absence of any locally recognizable lesions it is clear that random biopsies, even if multiple, may still miss the affected area. In this predicament the methods of Ayre and Novak have the advantage that they remove sampling tissue from the whole of the most likely site, namely, the junction of the two different types of epithelia. In some cases the localization of the malignant area may be made before biopsy by means of the Schiller iodine test.

RADIOTHERAPY AND SURGERY IN CERVICAL CANCER

Although the diagnostic developments mentioned are likely to discover many cases of uterine cancer in its earliest phase, it must be recognized that probably for a considerable time the great majority of cases will remain of the active invasive type. The insidious nature of the growth, which is often for long relatively symptomless, will continue to defer diagnosis until the disease has reached a late stage. Nevertheless, it is still true that many patients have the typical history of irregular bleeding, often provoked by coitus, occurring round about or after the menopause, which has existed for months before they have sought advice or received from their doctor the appropriate investigation.

The treatment of cancer of the cervix rests between radiotherapy and surgery, and it is a somewhat strange coincidence that the over-all efficacy of these two such divergent methods has proved to be so similar. Either method in good hands has been able to promise in cervical cancer a five-year survival rate, with freedom from disease in about 25 to 30 per cent. of all cases seen. Victor Bonney's (1949) results for the Wertheim's operation show that out of every 100 cases he has only operated on 63 per cent., and out of the total 100 cases he has a 25 per cent. survival rate. In the Radiumhemmet at Stockholm (1948), out of every 100 cases seen, 95 were treated, with a survival rate of 28.8 per cent. Thus, whilst the maximum effort of treatment is expended in cases chosen for radiotherapy, in 37 per cent. of the cases in the surgery group further treatment is still available, and for them radiotherapy still has its chance. It is true that the majority of these

followed in six weeks by the removal of the whole uterus, with the tubes and ovaries. Heyman (1947) has made a strong plea, supported by large figures, for radiotherapy as the primary method in corporeal cancer, with surgery reserved for cases failing to respond. His five-year survival rate without evidence of disease was 363 out of 698 cases, or an absolute cure rate of 52 per cent. In 49 patients, hysterectomy, sometimes of the supra-vaginal type, was carried out because of a poor response to radiotherapy. In the clinically operable the cure rate was 67 per cent., in the "technically operable" cases (in which, although operable, the risk was too great) the rate was 48 per cent., and in the inoperable it was as high as 28.7 per cent. Heyman's record extends over the years 1914-39.

Since 1930 the technique at the Radiumhemmet at Stockholm has consisted of a sufficient number of radium containers—either tubes with 8 mg. element or needles with 10 mg. element, each with a filter equivalent to 1 mm. lead—to pack the uterus completely. Two treatments are given with an interval of three weeks, and a total dosage of 3000 mg. element hours. The relative cure rate (i.e. five-year survival with freedom from disease in cases treated) in the 1914-33 group of 354 cases was 45 per cent., whereas the rate in the 1934-39 group, treated by the improved technique and comprising 316 cases, was 64.9 per cent.

These figures are impressive. Heyman believes that they show that primary radiotherapy followed by hysterectomy in case of failure is superior to hysterectomy as the primary choice. At the same time, as he points out, it still leaves undecided, and there are no adequate figures available to settle the question, how far improved results might be obtained in operable cases by primary surgery followed by irradiation.

References

- Ayre, E. (1948): *J. Amer. med. Ass.*, **136**, 513.
 Bonney, V. (1949): *Lancet*, **i**, 637.
 Brunswick, A. (1948): *Bull. N.Y. Acad. Med.*, **24**, 672.
 Fremont-Smith, M., Graham, R. M., and Meigs, J. V. (1947): *New Engl. J. Med.*, **237**, 302.
 Galvin, G. A., and Te Linde, R. W. (1949): *Amer. J. Obstet. Gynec.*, **57**, 15.
 Glucksmann, A., and Spear, F. G. (1945): *Brit. J. Radiol.*, **18**, 313.
 —, and Way, S. (1948): *J. Obstet. Gynec. Brit. Emp.*, **55**, 573.
 Graham, R. M. (1947): *Surg. Gynec. Obstet.*, **84**, 166.
 Heyman, J. (1947): *Brit. J. Radiol.*, **20**, 85.
 Isbell, N. P., et al. (1947): *Amer. J. Obstet. Gynec.*, **54**, 576.
 Novak, E. (1948): Quoted from "Yearbook of Obstetrics and Gynecology", Chicago, p. 476.
 Papanicolaou, G. N., and Traut, H. F. (1943): "Diagnosis of Uterine Cancer by the Vaginal Smear", New York.
 Pund, E. R., and Auerbach, S. H. (1946): *J. Amer. med. Ass.*, **131**, 960.
 —, Nettles, J. B., Caldwell, J. D., and Nieburgs, H. E. (1948): *Amer. J. Obstet. Gynec.*, **55**, 831.
 Radiumhemmet (1948): "Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix", Stockholm.
 Scheffey, L. C. (1949): *Amer. J. Obstet. Gynec.*, **57**, 33.
 Stevenson, C. S., and Scipiadès, E. (1938): *Surg. Gynec. Obstet.*, **66**, 822.
 Taylor, H. C., and Guyer, A. B. (1946): *Amer. J. Obstet. Gynec.*, **52**, 451.
 Warren, S., Meigs, J. V., Severance, A., and Jaffe, H. L. (1939): *Surg. Gynec. Obstet.*, **69**, 645.

would be of great value to the radiotherapist. The selection of those cases which are resistant to radiotherapy would make possible the mobilization for them at an early stage of the resources of surgery.

In the past, several attempts have been made to obtain information on this question. Thus Warren *et al.* (1939), in the United States, published a report of 70 cases of carcinoma of the cervix studied by means of repeated biopsies during radiation treatment. They found that if there was a marked radiation effect, the survival rate was increased, whilst with a poor effect the prognosis was poor. But the work of Glucksmann and Spear (1945) was the first attempt to lay down a set of more or less constant and measurable criteria by which the response of the tumour to radiotherapy could be foretold. These histological criteria had been employed during a period of two to five years and had in 90 per cent. of cases been borne out by the subsequent clinical course. The procedure is based upon the comparison of the population of the various kinds of cells in the growth before the institution of treatment and one week after treatment is started: "In favourable cases no normal mitotic cells should be found seven days after the first radium insertion and the percentage of resting cells should have fallen to below 30; while the percentage, particularly of differentiating, but also of degenerating, cells, should have risen correspondingly".

Glucksmann and Way (1948) have recently published a review of 149 cases so studied between December 1946 and June 1948. In 88 the cytological response was unfavourable and these included 64 which by staging (stages I, II, III) were operable. For a number of reasons (concomitant disease, advanced age) only 38 of these cases were suited for operation and of these the Wertheim's operation was actually completed in 28. The cases are naturally too recent to allow of any conclusions regarding ultimate results.

Glucksmann and Way employ biopsy for the purpose of their assessment. Graham (1947) has in 73 cases of cervical carcinoma studied the response to radiation by means of the vaginal smear and has claimed a prognostic accuracy of 88 per cent. One-third of her stage II cases showed no radiation response. This gave an index of the possible value of the smear for the evaluation of the clinical material from the standpoint of surgery. This author claims that the vaginal smear has some advantages over biopsy in that it is simpler and is more likely to provide a general assessment of the cytological changes than the biopsy, which depends for its accuracy upon the proper selection of the site. In some instances this may fail to hit the proper area.

CARCINOMA OF THE UTERINE BODY

During the past decade the method of election in most clinics for the treatment of carcinoma of the body of the uterus has been surgery, with a relative five-year cure rate of between 48 and 55 per cent. Radiotherapy has in general been reserved for those unsuited for operation by reason of the advanced stage of the disease, because of poor operative risk or as a routine in the postoperative attack on the pelvic glands. In some clinics improved five-year survival rates have been claimed for irradiation (X-rays or radium)

Treatment.—A doctor in charge of a girls' school reported that a number of pupils in the junior section complained of pains at the menstrual periods. Those who complained were encouraged to play games, to stop brooding, and to live active lives. The number complaining in the intermediate school was much lower, whilst in the senior school only a very limited number had any discomfort. This natural cure should be borne in mind, as mothers are naturally anxious and will worry until reassured. Simple measures, such as attention to general health, regularity of the bowels, possibly aspirin, veganin, and even bromides may be tried. Potent drugs such as morphine, or its derivatives such as pethedine, and alcohol in any form should be avoided.

The girl who appears at an out-patient clinic, who is a clerk or typist or domestic worker, and states that she has to leave her work at the time of the period must be treated radically. If she loses her job as a result of her disability she will brood and become introspective and finally a hopeless neurotic. The operation of choice is a *dilatation* with Hegar's dilators. A curetting is never done unless there are heavy losses at the periods or some suspicion of the presence of an intra-uterine polypus. Size 8 is the usual maximum and the results obtained are nearly always successful. In some patients the relief is temporary, possibly for only a month or two. A further dilatation may be tried but the causes of failure of the primary operation must be considered. The following should be kept in mind:—

(1) The dilatation has been imperfectly done. The internal os has not been dilated but only the cervical canal as far as the internal os. Meeting with difficulty at this point the operator may desist rather than risk perforating the uterus. This is corrected by dilating the cervical canal as far as the internal os up to no. 8 Hegar and then starting again with the smallest size, which will almost certainly pass the internal os, and a complete dilatation can then be performed.

(2) Hegar's dilators are crudely graded, and when the cervical tissues are very rigid the tension with the volsellum is such as to risk tearing the cervix; hence an incomplete dilatation of the internal os. (Murray, E. Farquhar: *J. Obstet. Gynec. Brit. Emp.*, 1948, 55, 72.)

I am fortunate to possess a set of Hegar's dilators which the late Professor Leith Murray had made specially. In several virginal uteri he has dilated to the maximum 36, which is equal to no. 16 Hegar, and the dilatation is such that the interior of the uterus can be palpated. With such superdilatation several cases which could not be relieved by the routine operation have obtained complete relief.

In some cases which are quite intractable to these measures there is still the procedure of *presacral neurectomy* to be considered. This is most successful in a number of cases, but not invariably. The desire to avoid opening the abdomen is natural but the operation must be considered. I have been informed of a case in which even hysterectomy has not relieved the patient of her complaint.

THE PROBLEM OF DYSMENORRHOEA

By E. FARQUHAR MURRAY, M.D., F.R.C.S., F.R.C.O.G.

Professor of Midwifery and Gynaecology, University of Durham; Consulting Gynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne.

IN this article I do not propose to deal systematically with a subject which is much too vast and complex to be discussed in a single article. Rather do I propose to concentrate upon certain practical aspects of the problem as I have seen them in practice.

Dysmenorrhœa is divisible into two well-defined groups—the spasmodic and the congestive. In the former the pain is fairly acute and short-lived, starting with or near the onset of the menstrual period and lasting some hours or even during the whole time of the period. It is referred to the lower abdomen on both sides, and in some cases is associated with vomiting and bladder or bowel irritability. In the latter there is pain during the phase of premenstrual congestion and this pain reaches its peak during the flow and slowly retrogresses, but does not cease for some days after the menstrual loss has ceased. The congestion is often accompanied by menorrhagia. This is seldom met with in the spasmodic type.

SPASMODIC DYSMENORRHOEA

This is the usual form complained of by young girls. It may have been present since puberty, but this is not always the case, as the pain may develop after the girl has menstruated for some years without discomfort. There is usually a degree of hypofunction, as expressed by scant menstrual flow for the usual number of days or for only a few days, or even merely a trace for one day. Sometimes there are gaps of one or two months between the periods. The secondary sexual features, such as the breasts and pubic hair, may appear less developed than the average, but this is not usually a common feature. A pelvic examination made either per rectum or per vaginam (under anæsthesia) shows numerous signs of under-development or atypical development: the infantile uterus—or the small uterus with a conical cervix—or one that is acutely anteflexed or retroflexed, or some such modifications. It is important to bear in mind that many girls with such pelvic findings and possibly scant menstrual loss have no discomfort at their periods. Nevertheless, such uteri are more likely to be associated with spasmodic dysmenorrhœa than those normally developed, and when the menstrual loss is normal in amount and periodicity. The kink of an acute anteflexion with the conical cervix and pinhole os has led to the pain being attributed to some obstructive factor. This may occasionally be the case, as some patients report that the pain is severe if they are passing clots.

It is important to bear in mind that when a young married woman complains of spasmodic dysmenorrhœa, what she is really anxious about is her delay in having a baby. Such women are subfertile.

merely a bulky and mobile parous uterus, the term subinvolution suffices. If a laparotomy has been performed it is surprising to note how many such uteri which come under the term of subinvolution show patches of healed plastic peritonitis and numerous transparent veil-like adhesions which are impalpable and which do not in any way restrict the mobility of the uterus. Such cases at an out-patient clinic are those unhappy regulars who come back complaining that they are no better and still have their ache and pains, especially at the menstrual periods which are associated with heavy, even "drenching" losses. The patient may be in her early thirties and quite anxious to have another baby, hence the conservative treatment. When, however, she can stick it no longer or is becoming a chronic invalid something radical must be done.

Treatment.—The nervous patient who exaggerates her pelvic congestion should be treated on general tonic lines. A dilatation may be tried. Cases with a urinary element should have this actively treated, primarily with citrates or a course of sulphacetamide. The question of renal lavage is outside the scope of this article. When there is gross evidence of pelvic mischief, such as thickened tubes or an adherent and tender uterus, the case is one for operation, the details being left to the operator.

The most difficult case of all is the woman in whom there is doubt as to what is the cause at work—urinary inflammation or pelvic mischief, or both. In such cases no definite proof of pelvic inflammation has been found. The uterus is mobile and the tubes not thickened. In such, especially if there are no heavy losses, it is well to act cautiously. The urinary and possibly nervous element should be treated actively, and such a common mixture as one of citrates and bromides may work wonders. All the skill of the genito-urinary experts may be invoked to solve this matter. When no relief is obtained, then in cases with a completely negative pelvis it is sometimes helpful to inject the uterus and tubes with lipiodol or one of its substitutes. Radiography may show that the tubes are blocked or fibrosed, and this settles the matter: i.e., there is impalpable pelvic mischief which provides justification for advising a laparotomy.

When trying conservative measures it is justifiable to curette the uterus in cases with menorrhagia; this does not readily lessen the discomfort but it may conserve blood loss which can soon make an invalid of a woman. A dilatation alone is of course quite futile in these cases.

Endometriosis is an occasional cause of severe congestive dysmenorrhœa. The endometrial implants on the ovary lead to the formation of chocolate or tarry cysts on that organ. The pain at each period is tensile due to menstrual fluid being secreted into the cyst and is usually markedly unilateral, and a mass is readily palpable. Endometriosis is sometimes more diffuse and scattered over the pelvic peritoneum, and invades the rectovaginal septum. There is no gross mass, but usually some thickening of the pelvic peritoneum can be detected with fine nodulation in the pouch of Douglas. Treatment is usually operative, but radium has been used in some cases.

Organotherapy is so disappointing that discussion of it is purposely left until the last. Œstrin given to stimulate uterine growth and function seems reasonable, but nature does this herself in young women. Progesterone to quieten the excitable uterus also commends itself, but it does not have the measure of success that the manufacturers predict. Marriage has been advised as a solution: surely if anything could stimulate the hormones of any woman this should. Intercourse either produces no relief or aggravates the condition, whilst the uterus dilated to the extent to allow a baby to pass may not infrequently leave the woman with her pain and discomfort when her periods return after convalescence.

A true case of spasmodic dysmenorrhœa requiring morphine was a single woman in her early thirties who had a submucous intra-uterine fibroid. The history and the pelvic examination made the diagnosis obvious, and a hysterectomy being necessary, the symptoms disappeared.

CONGESTIVE DYSMENORRHŒA

Congestive dysmenorrhœa is a much larger problem and many factors must be considered. The mere physical fact of congestion leading up to, and during, menstruation is no doubt sensed by even a normal woman, as few are entirely free from a measure of discomfort at these times, but she is able to ignore its presence. If, however, she is run down, constipated, nervous and introspective she allows this phase to dominate the picture and make its presence felt, just as a nervous male may complain bitterly of the ache caused by a varicocele of the testis. Operations for ligating the ovarian veins have been performed, but the vogue is now almost obsolete.

If any form of pelvic inflammation is normally the cause of discomfort this will be increased markedly at the menstrual periods. One of the frequent causes is infection of the urinary tract with tender ureters, and almost certainly of the bladder also. More commonly there is genuine inflammatory trouble connected with the uterus, tubes or ovaries which is due to infection arising after an abortion, or a confinement. It is possible to have a urinary infection alone, but it is impossible for a patient with genuine inflammation of the uterus and tubes not to have a urinary infection as well.

Some points here require amplifying. Pelvic inflammation may have an appendical or tuberculous origin. The first is usually fairly obvious but the latter is often a matter of conjecture and may date from some illness in childhood, variously diagnosed as congestion of the bowels or enteritis, and a prolonged period in bed. Cases of extra-genital causative foci are not usually associated with menorrhagia, which is a common association with cases of genital inflammation, either post-partum or post-abortal. A surprising number of cases proved to be due to genital sepsis give no clear-cut history of having such an active septic state about the time of an abortion or confinement. If one is forthcoming, so much the better.

The examination of the pelvis may give gross proof in the form of thickened tubes or a somewhat fixed and bulky uterus. The term "chronic metritis" is often applied to the uterus in such cases, but when the uterus is

merely a bulky and mobile parous uterus, the term subinvolution suffices. If a laparotomy has been performed it is surprising to note how many such uteri which come under the term of subinvolution show patches of healed plastic peritonitis and numerous transparent veil-like adhesions which are impalpable and which do not in any way restrict the mobility of the uterus. Such cases at an out-patient clinic are those unhappy regulars who come back complaining that they are no better and still have their ache and pains, especially at the menstrual periods which are associated with heavy, even "drenching" losses. The patient may be in her early thirties and quite anxious to have another baby, hence the conservative treatment. When, however, she can stick it no longer or is becoming a chronic invalid something radical must be done.

Treatment.—The nervous patient who exaggerates her pelvic congestion should be treated on general tonic lines. A dilatation may be tried. Cases with a urinary element should have this actively treated, primarily with citrates or a course of sulphacetamide. The question of renal lavage is outside the scope of this article. When there is gross evidence of pelvic mischief, such as thickened tubes or an adherent and tender uterus, the case is one for operation, the details being left to the operator.

The most difficult case of all is the woman in whom there is doubt as to what is the cause at work—urinary inflammation or pelvic mischief, or both. In such cases no definite proof of pelvic inflammation has been found. The uterus is mobile and the tubes not thickened. In such, especially if there are no heavy losses, it is well to act cautiously. The urinary and possibly nervous element should be treated actively, and such a common mixture as one of citrates and bromides may work wonders. All the skill of the genito-urinary experts may be invoked to solve this matter. When no relief is obtained, then in cases with a completely negative pelvis it is sometimes helpful to inject the uterus and tubes with lipiodol or one of its substitutes. Radiography may show that the tubes are blocked or fibrosed, and this settles the matter: i.e., there is impalpable pelvic mischief which provides justification for advising a laparotomy.

When trying conservative measures it is justifiable to curette the uterus in cases with menorrhagia; this does not readily lessen the discomfort but it may conserve blood loss which can soon make an invalid of a woman. A dilatation alone is of course quite futile in these cases.

Endometriosis is an occasional cause of severe congestive dysmenorrhœa. The endometrial implants on the ovary lead to the formation of chocolate or tarry cysts on that organ. The pain at each period is tensile due to menstrual fluid being secreted into the cyst and is usually markedly unilateral, and a mass is readily palpable. Endometriosis is sometimes more diffuse and scattered over the pelvic peritoneum, and invades the rectovaginal septum. There is no gross mass, but usually some thickening of the pelvic peritoneum can be detected with fine nodulation in the pouch of Douglas. Treatment is usually operative, but radium has been used in some cases.

THE CARE OF THE MENOPAUSAL WOMAN

By T. N. MacGREGOR, M.D., F.R.C.S.Ed., F.R.C.O.G.

Assistant Obstetrician and Gynaecologist, Royal Infirmary, Edinburgh.

THE menopause signifies the end of menstrual and reproductive life. It occurs most often between the ages of forty-five and fifty, but it may occur at a considerably earlier age or may be delayed for several years. The duration of menstrual life is largely influenced by hereditary factors. It has been observed that there is often a relationship between the time of onset and the time of cessation of menstruation; the later the menarche the earlier the menopause, and conversely, the earlier the menarche the later the cessation of menstrual function.

The popular conception of the menopause was, until within recent times, shrouded in superstition and based largely on folklore. The terms "change of life" and "critical age" which have been, and still are, employed to describe this phase are in themselves unfortunate as they premise something mysterious and foreboding. This concept is gradually being superseded, however, by a more enlightened outlook amongst women and by the growing realization, based on scientific data, that the cessation of menstrual and reproductive function need not cause any profound change in a woman's mode of life.

Menstruation ceases when the hormonal and ova-producing potentiality of the ovaries has been exhausted. The ovaries, having fulfilled their physiological purpose, become senile and no longer function as organs of internal secretion. The ageing of the ovaries is a gradual process which takes place over many months or even years, so that the endocrine system is able to adjust itself to the absence of the ovarian secretions. The transitional phase, or period during which the endocrine balance becomes adjusted, is termed the climacteric and may be associated with vasomotor, nervous and metabolic disturbances so marked as to form a definite syndrome. Whilst the majority of women pass through the climacteric with very little discomfort, others are harassed by severe manifestations and require treatment. An appreciation of the manifold changes which occur at the menopause and their significance in regard to the symptomatology is essential for the intelligent management of the menopausal patient.

The cessation of menstruation is the most outstanding feature of the climacteric. It is normally a gradual process, the interval between the menses becoming progressively more prolonged and the menstrual loss more scanty before menstruation finally ceases. Abrupt cessation of menstruation without any preceding change in the rhythm or amount of menstrual loss is uncommon. Sometimes the menopause is heralded by episodes of excessive blood loss either at regular or prolonged intervals. Intermenstrual bleeding and excessive loss are abnormal and are usually

indicative of some pathological lesion. There is no justification for the administration of any hormone preparation to control the irregular bleeding until a thorough investigation, including curettage of the uterus, has been carried out. The incidence of carcinoma of the cervix is so high during the fifth decade of life that it is always advisable to consider the advent of irregular uterine bleeding at this time as being due to carcinoma until this has been excluded by curettage. Thus the presence of malignant disease can be detected at a stage when the outlook for treatment is much more favourable.

THE MENOPAUSAL SYNDROME

Hot flushes constitute the most characteristic and constant subjective symptom of the climacteric. They are sensations of heat which pass over the face, neck and upper part of the trunk; localized areas of flushing may be manifest, especially on the face and neck. They last for from a few seconds to several minutes and may be accompanied or followed by profuse sweating and succeeded by a sensation of chilliness. These vasomotor phenomena, which vary in their frequency and severity, are rarely entirely absent, but may be so evanescent as to pass unnoticed; they may occur only once, twice or three times per day or as often as forty to fifty times in the twenty-four hours. Frequent and severe hot flushes may interfere with sleep and cause considerable distress and apprehension. Generally they become manifest after the menopause, sometimes for the first time years after the menopause, but may appear in a mild form some considerable time before the cessation of menstruation.

Headache, vertigo, insomnia, palpitation and dyspnoea are common. Many women tend to be irritable, are readily upset and may become unreasonable, apprehensive and depressed. The symptoms which may arise can be so diverse as to simulate those of almost any systemic disease. It is recognized that organic lesions related to the heart, blood vessels, kidneys and pelvic organs are prone to become manifest during this phase of life, and it is therefore important that organic disease should be excluded by a thorough physical examination before assuming that the symptoms are climacteric in origin.

Although the menopausal syndrome is primarily due to the cessation of ovarian activity, other factors, such as the overactivity of the anterior pituitary which is secondary to the ovarian senescence, and the nervous reactions which often supervene, are of significance in the production of the symptomatology.

It is difficult to assess the importance of the psychosomatic factor. Women view the menopause in different ways. To many, especially those who have had large families, the cessation of menstruation comes as a welcome relief as they are no longer haunted by the constant worry and anxiety of further child-bearing. Others who have suffered for years from

menstrual discomfort long for the relief which the menopause brings and the new lease of life which it often means. On the other hand, many women view the climacteric with considerable fear and apprehension. They see it not merely as the end of menstrual life but the beginning of a new phase which they anticipate as being unpleasant. They dread the possibility of an increase in weight, loss of attractiveness and decline in sexual responsiveness. Others, who have longed for motherhood, appreciate the significance of the advancing years and react unfavourably to the occurrence of any untoward symptoms.

GENERAL MANAGEMENT

The manifestations of the menopausal syndrome are so varied that although a general scheme of management can be outlined, it must be recognized that each case requires to be assessed individually in regard to specific treatment. Many women derive considerable benefit and reassurance from a simple explanation of the significance of the menopause, and in this respect there are several points which require special emphasis. The importance of outside interests, adequate exercise and rest, and a well-regulated diet should be stressed. Some women have a tendency at this time to be less careful of their personal appearance, to indulge in over-eating and to relax and consolidate past achievements, but this should be discouraged if they wish to retain, in the autumn of life, something of the vigour and interest of their earlier years. It should be emphasized that sexual desire does not necessarily diminish with the cessation of menstruation; indeed, it may increase. The continuation of marital relationships after the menopause depends upon several factors, such as previous sexual life, the husband's attitude and the patient's own reactions.

Minor menopausal symptoms, such as infrequent hot flushes, insomnia, irritability and depression, usually respond to treatment along the general lines already advocated, supplemented, if necessary, by the administration of a mild sedative, such as $\frac{1}{2}$ a grain (32 mg.) of phenobarbitone night and morning. This form of treatment is particularly helpful when minor symptoms arise before the cessation of menstruation, a time when it is doubtful whether oestrogen therapy is either indicated or desirable.

OESTROGEN THERAPY

Severe symptoms, especially frequent hot flushes, occur only in a minority of menopausal women. The administration of an oestrogenic preparation is specific and controls the symptoms within a short time. The immediate control of the flushes—and in this respect the oestrogens have been a veritable boon to many women—has a beneficial psychological effect and, as a rule, changes the patient's whole outlook. She rapidly regains a feeling of well-being, is able to concentrate and carry on with her daily routine and, what is probably of major importance, she is able to enjoy undisturbed sleep. The maximum benefit is obtained if an adequate amount of hormone,

depending upon the severity of the symptoms, is administered initially and then the dosage gradually reduced. Apart from the immediate control of the symptoms, an adequate dosage of oestrogen to begin with restores in some measure the hormonal balance, and its gradual reduction permits the endocrine system to adjust itself to the absence of the ovarian secretions.

Various *methods of administration* of the oestrogenic hormone are employed; it may be given intramuscularly, orally or by pellet implantation. These are all equally effective provided a potent preparation is used. The natural hormones of the ovary were employed almost universally until within recent years. They were most often administered as oestradiol benzoate, in doses of 5 mg. daily, until the symptoms were controlled, and thereafter every third or fourth day for two weeks, followed by a weekly injection for a further two or three weeks. This method of treatment has largely been displaced by the introduction of synthetic oestrogenic preparations which are relatively inexpensive and are as effective orally as the natural oestrogens by intramuscular injection. The synthetic preparations, stilboestrol, hexoestrol and dienoestrol, bear no chemical relationship to the naturally occurring hormones but are potent oestrogenic substances. They have the disadvantage that they sometimes produce, even in small doses, toxic manifestations such as nausea and vomiting, and their administration may have to be discontinued on this account. Recently, another synthetic oestrogen—ethinyl oestradiol—a derivative of the natural follicular hormone, has become available for clinical use. This preparation is probably the most potent oestrogen so far produced, and it has a slight advantage over the stilbene derivatives such as stilboestrol in that it has not the same tendency to produce side-effects.

The *dosage* of synthetic oestrogen required to control menopausal symptoms must be suited to the needs of the individual. When the symptoms are severe, large doses are indicated, whereas mild symptoms can be controlled by a considerably smaller dose. The following course of treatment is suggested for the control of severe symptoms: ethinyl oestradiol in doses of 0.05 mg. (or stilboestrol, 5 mg.), thrice daily until all the symptoms are controlled; this usually occurs in three to five days. Thereafter 0.05 mg. is given daily for seven days and the same dose every second day for a further week, then the interval between each dose is increased until by the eighth week only one tablet is being taken weekly. Generally no further treatment is required. When the symptoms are mild, an initial dosage of 0.05 mg. ethinyl oestradiol daily for two to three days, gradually reduced over the next seven or eight weeks, is usually sufficient.

Theoretically the administration of oestrogen by *pellet implantation* seems reasonable as there is slow absorption with a gradual decline in the amount of hormone passing into the circulation. Oral therapy, however, is adequate and can be controlled so readily that pellet implantation, which does involve a small surgical technique, is rarely indicated.

The administration of œstrogen, especially if it is prolonged, reactivates the uterine endometrium in a proportion of cases and bleeding occurs when the œstrogen is reduced or withdrawn. Every patient having œstrogen therapy should be warned that such a complication may arise, otherwise it may cause considerable alarm, especially if it occurs some time after the menopause. The occurrence of the bleeding always raises the problem in the mind of the physician as to whether it is due to an œstrogenic effect or is symptomatic of uterine malignancy. Bleeding due to malignant disease will recur, but œstrogen-induced bleeding subsides very quickly after treatment has been suspended. It is therefore advisable to stop all treatment if bleeding supervenes and keep the case under review; if the bleeding recurs, malignancy must be excluded without delay by a detailed investigation of the reproductive tract, including curettage of the uterus.

REGRESSIVE VAGINAL CHANGES

Regressive changes occur in the reproductive tract after the cessation of ovarian function; the changes affecting the vulva and vagina are of special importance as they predispose to conditions such as senile vaginitis, kraurosis vulvæ and leucoplakia vulvæ.

Senile vaginitis is an inflammatory condition of the vaginal mucosa due primarily to the œstrogen deficiency. The vaginal walls, which are thin and atrophic, have a characteristic congested appearance and scattered over them are small deep red areas of granulation tissue. The main symptoms are irritation, pelvic discomfort, dyspareunia and a leucorrhœal discharge which is sometimes blood-stained. Senile vaginitis responds favourably and quickly to the administration of high doses of œstrogen. Five milligrammes of stilbœstrol, or 0.05 mg. of ethinyl œstradiol, thrice daily over a period of ten days, usually alleviate the symptoms. This treatment can be supplemented by the local administration of œstrogenic hormone in the form of pessaries. One pessary should be inserted into the vagina every second night for a period of two to three weeks.

Kraurosis vulvæ, which is common at the menopause, is characterized by shrinkage and atrophy of the vulvar tissues, affecting particularly the labia minora, vestibule and clitoris. In the early stages these structures have a reddish appearance; later they assume a distinctive yellowish coloration. The symptoms usually associated with kraurosis are irritation, dysuria, painful coitus and an ache in the vulva. The vulvar atrophy, although closely related to œstrogen deprivation, does not always respond to intensive œstrogen therapy. This form of treatment, however, should always be given a trial in the first instance, administered along the lines advocated for senile vaginitis. The application of sedative lotions or 5 per cent. cocaine ointment is sometimes helpful when the œstrogens are ineffective. A plastic operation designed to increase the size of the vaginal introitus is sometimes necessary for the relief of the dyspareunia.

Leucoplakia vulvæ is probably also a manifestation of the disturbed endocrine balance which occurs at the menopause. The condition is characterized in the early stages by redness of the vulva which later assumes a distinctive dull white appearance; the tissues become thickened and furrowed; cracks and fissures are prone to occur. The leucoplakia may involve only a small area of one or other labium but is generally extensive and may involve the whole vulva, apart from the vestibule, and spread on to the perineum. Intense and sometimes intolerable irritation is the characteristic symptom. The importance of this condition is that it strongly predisposes to carcinoma of the vulva, and although the irritation may sometimes be relieved by oestrogen therapy, this form of treatment should not be continued for any length of time if there is no improvement. Operative treatment in the form of vulvectomy should not be delayed indefinitely, as it is justifiable and sound treatment for the condition and a prophylactic measure against the development of malignant disease.

OTHER CLIMACTERIC MANIFESTATIONS

Apart from the vasomotor phenomena and local pelvic lesions, other manifestations of oestrogen deficiency occurring at the climacteric which require consideration are menopausal psychosis, arthritis and hypertension.

Menopausal psychosis.—Mild depression is a common feature of the menopausal syndrome and in the majority of cases responds satisfactorily to simple measures. There are, however, some cases, especially those with an unsound hereditary background, which react unfavourably to the menopausal disturbances and become definitely psychotic. Much can be done by encouragement, sedatives and oestrogen therapy to tide these patients over this crisis, but institutional treatment is sometimes necessary. The duration of hospitalization may be appreciably shortened by a continuation of oestrogen therapy.

Menopausal arthritis.—A small proportion of women develop a mild form of arthritis at the menopause. The arthritic changes affect particularly the knee joints, which become swollen and painful. There is some evidence to suggest that the arthritis is due to vascular changes in the joints subsequent to the cessation of ovarian function. Oestrogen therapy in the early stages may prove beneficial and should certainly be employed as an adjuvant to other forms of treatment.

Menopausal hypertension.—Hypertension, varying in degree, may appear for the first time at the climacteric. The blood pressure is usually labile; the systolic pressure rarely exceeds 170 mm. Hg and may vary from day to day. There is no unanimity of opinion as to the cause of menopausal hypertension. It is often a temporary phenomenon and therefore may be related to the endocrine imbalance. Oestrogenic therapy should always be considered in the management of such cases.

PRURITUS VULVÆ

By JOCELYN MOORE, M.B., F.R.C.S., F.R.C.O.G.

Obstetrician and Gynæcologist, Royal Free Hospital, and to the South London Hospital for Women.

IRRITATION of the vulva in the form of itching or burning is symptomatic and is not a disease *per se*. It may, however, be found in association with a large variety of morbid conditions and be accompanied by various other symptoms. Sometimes in cases with severe pruritus no local morbid condition of the vulva or adjacent soft parts can be seen in the early stages; but later, when severe irritation leads to scratching or rubbing with superimposed infection, local changes do occur which may obscure the original affection. The areas most commonly involved are the labia majora and minora; the clitoral region, the perineal, peri-anal and natal folds may also be affected. It may be met with at all ages, but is most commonly present in the older age-groups. In the milder cases the irritation is noticed mainly at night or in hot weather. However, all grades of severity may be met with; in the most severe there may be constant and almost intolerable itching during both day and night.

PATHOLOGY

Veit has described a definite pathological entity, parakeratosis, as characteristic of pruritus vulvæ. In this condition it can be seen microscopically that processes of keratinized epithelium dip down into the corial layer and become surrounded by a definite zone of leucocytic infiltration. The general consensus of opinion, however, is that this microscopic appearance results not as a precursor of pruritus but as a result of the continued rubbing and scratching, with secondary infection of the skin. More specific pathological changes are seen in kraurosis vulvæ and leucoplakia, which will be discussed later.

CAUSATION

Many local and general conditions may give rise to the symptom of itching. These can be classified briefly as falling into four main groups:—

- (1) Vaginal discharges of acute or chronic origin which may actually produce irritation of the mucous membrane of the vulva.
- (2) Local diseases of the vulva.
- (3) General toxic conditions.
- (4) Psychoneuroses.

VAGINAL DISCHARGE

Discharges in the acute stage of infection, such as in gonorrhœa, do not usually result in pruritus, the sole exception being in *Trichomonas vaginalis*

infection, in which intense irritation may be an early symptom. This irritation is due partly to the highly acid secretion associated with the infection, and partly to the actual active motility of the protozoa. It is, however, with the chronic discharges that the symptom of pruritus is most commonly associated. These may be the result of chronic gonorrhœal, trichomonal, or monilial infections, or from the retention of a rubber ring pessary used in the treatment of prolapse. The constant dribble of urine in cases of stress incontinence, or vesico-vaginal fistula with secondary mucosal and skin infection may produce a similar lesion. In children, threadworms originally present in the anal canal may pass forward to become lodged in, and infect, the vaginal canal. Pediculosis, or complete lack of personal hygiene may also produce much the same effect as actual vaginal discharge.

LOCAL DISEASES OF THE VULVA

It is in this group that the symptom of pruritus is most commonly encountered. The conditions most often seen are those of intertrigo, eczema, kraurosis and leucoplakia.

Intertrigo usually affects obese women, particularly those in whom personal cleanliness is lacking and those in whom stress incontinence is present. Sweating during hot weather often precipitates an attack. Intertrigo is seen as a superficial redness of the labia majora spreading to the pubic region and inguinal, genito-femoral and natal folds. Intertrigo does not affect the actual mucosal surfaces.

Eczema.—This is a true dermatitis usually beginning as a localized papular rash involving the inner surface of the labia majora and outer surface of the labia minora. Exudation from the papules quickly follows, leaving a moist red surface. In the acute cases this papulo-erythematous area rapidly spreads to the whole of the pubic and perineal surfaces, and in some instances extensive areas of the thighs may be involved. In the long-standing cases the affected areas become dry and scaly with hypertrophied epithelium. Secondary infection masking the original eczematous condition is common and is the result of persistent rubbing or scratching.

Kraurosis.—Berkeley and Bonney have described kraurosis as "an atrophic condition of the vulva associated clinically with stenosis of the vaginal orifice and pathologically with certain changes in the dermis". In other diseases of the vulva, notably leucoplakia, atrophic processes may also be observed. The normal prototype of pathological kraurosis is seen in the atrophy of the vagina and vulva taking place in all women at the time of the menopause. A more obvious form occurs after oophorectomy or after radium treatment, used either to induce an artificial menopause, or in the treatment of cervical or fundal carcinoma. The atrophic changes of the menopause are normally moderate in degree, but occasionally are extreme. Subcutaneous fat in the labia majora disappears so that they become small or flat and the skin thin, glazy in appearance and reddened. The labia

minora likewise atrophy and the clitoris becomes small and almost disappears. With these changes there is a marked narrowing of the introitus making coitus difficult or impossible. The obvious explanation is that these kraurotic lesions result from the withdrawal of the œstrogenic trophic hormones. Kraurotic changes can also be seen in younger women with apparently normal menstruation. In these it can only be supposed that the vulval tissues have lost their responsiveness to the ovarian hormones. It is easy to see how this thin epithelial surface would become liable to infection through any abrasion of the skin surface. Adair and Davis have called attention to this secondary change, characterized by the development of a true dermatitis, and clinically by the predominance of pruritus as a symptom. The skin infection in these cases passes from the acute stage of redness and swelling to the chronic stage of induration and keratinization, and may even show a leucoplakic tendency. In the absence of secondary infection the tissues remain retracted and thin. The colour changes to pale yellow with a glistening smooth surface. In these there is no tendency towards malignancy.

Leucoplakia.—The etiology of leucoplakia is unknown. It affects women of menopausal or postmenopausal age. Berkeley and Bonney have defined leucoplakia as "a chronic inflammatory condition characterized in its early stages by hyperæmia and cellular activity, and in its later stages by epithelial hypertrophy and a thickened sclerosed and retracted condition of the subepithelial tissue". The vestibule and orifice of the urethra are never affected, which is a point in the differential diagnosis between leucoplakia and kraurosis. The disease may spread laterally to the thighs and posteriorly round the anus.

Leucoplakia has been divided into four clinical stages. In the first stage the parts affected are red, œdematous and excoriated, with a raw, dry surface. Secondly, the labia become retracted due to the subepithelial thickening. The colour changes from red to white—hence the term leucoplakia. In the third stage, cracks and ulcerations are found, which may bleed. Carcinoma may develop at the base of a crack or ulcer. It is during the second and third stages of leucoplakia that pruritus is present. In the fourth stage, or atrophic phase, the involved area becomes smooth, shiny and white. In this last stage the atrophy of the parts is complete and the disease quiescent. The great importance of leucoplakia apart from the very distressing symptoms which it produces, lies in the fact that there is a strong tendency towards the development of cancer. Approximately one-half of all cases of vulval carcinoma, according to Taussig, are preceded by leucoplakia of the vulva.

GENERAL TOXIC CONDITIONS

Cases of pruritus vulvæ falling into this group are most commonly seen in association with *diabetes* and pregnancy. In women with glycosuria the constant passage of sugar-laden urine soon produces a chronic inflammatory

condition of the tissues. Pruritus may at first be the only local symptom of glycosuria, but soon the labia become reddened and œdematous. Small ulcerations are frequently seen. Time and time again it is found that the unfortunate woman seeks relief of the irritation in the gynæcological department before a diagnosis of diabetes is made. The importance of routine testing of the urine for sugar in all cases of pruritus cannot be too strongly stressed. The actual cause of the vulvitis has been attributed to the irritant effect of the urine, the growth of organisms, bacillary or monilial, which are favoured by the acid medium of the urine, or to the local neuritic changes produced by the disease.

In *pregnancy*, pruritus may not produce any local lesion. Irritation is not solely confined to the vulva; the abdominal wall is a frequent alternative or an associated area. This affection is now regarded as being a symptom of true toxæmia of pregnancy, possibly associated with a vitamin B deficiency.

PRURITUS IN THE PSYCHONEUROSES

These cases of pruritus show no alteration in the affected areas except those resulting from rubbing and scratching. The subjects of this type are usually women of neurotic or hysterical personality. Masturbation in young adults may have been a contributory factor. Pruritus of this order may also be found present in older married women with unsatisfactory sexual lives. They can obtain satisfactory relief of sexual tension often amounting to a true orgasm by clitoral stimulation by rubbing. If this practice is persisted in, inflammatory changes follow; these are mainly seen in the clitoral area, but in the established and severe cases may involve the whole of the vulva.

TREATMENT

It is often extremely difficult to arrive at a diagnosis of the underlying cause of the pruritus. The routine testing of the urine will immediately segregate those of diabetic origin. The relief of symptoms is usually dramatic as soon as the regulation of the diet with or without insulin administration is instituted. In those cases with an associated vaginal discharge, routine urethral and cervical smears may demonstrate the causal *gonorrhœal infection*. A purulent, watery, frothy discharge is suggestive of a trichomonal infection, whereas with monilial infection the discharge tends to be white and curdy. Both these offending organisms can easily be diagnosed by the examination of a hanging drop of the vaginal discharge in saline, or by a stained smear of the vaginal secretion. A trichomonal vaginitis often masks the underlying primary gonorrhœal infection. Both *trichomonal* and *monilial infections* usually respond quickly to daily vaginal swabbing with 1 per cent. gentian violet in aqueous solution, followed by stovarsol vaginal compound, or acetarsol tablets inserted in the vagina at night. An alternative treatment for trichomonal infections is by daily vaginal painting with 1 per cent. picric acid, made up in solution containing 1 part of S.V.R. and 3 parts

water. Insufflation with picragol powder or picragol pessaries (silver picrate) daily are also effective. Chronic trichomonal infections are often difficult to clear: to prevent relapse, treatment should be continued for one week following the next three menstrual periods after the apparent cessation of symptoms. The high recurrence rate is usually seen when this precaution is not taken. In persistent trichomonal infections the examination of the centrifuged deposit from a catheter specimen of urine should be undertaken. A trichomonal cystitis will continue to act as the focus for future vaginal reinfections. Bladder infections can be cleared with the use of daily wash-outs with sodium bicarbonate and urinary antiseptics, such as potassium citrate.

Those cases with a *doubtful or unknown etiology*, and in which no local skin change is present, are difficult and disappointing to treat. Sedation at night, preceded by a hot alkaline bath, often gives relief. Cases with an underlying psychological basis receive benefit from psychological treatment. Cases of chronic eczema, kraurosis vulvæ and leucoplakia in the early stages, can be relieved by appropriate local treatment. Before any local treatment can be effective the patient must be made to realize that personal cleanliness is essential and scratching or rubbing should be avoided. Scratching and rubbing are often done subconsciously at night, so in all but the mildest cases the wearing of soft cotton gloves and the administration of a sedative are advised as a routine.

The effect of local applications of lotions and ointments is varied: what may succeed in one case may be useless in another. Lotions such as sodium bicarbonate, 120 grains (8 g.) to the pint, 5 per cent. carbolic acid, or lead and opium lotion are the most effective. Calamine lotion, except in the "moist" eczema cases, tends if anything to increase the pruritus by producing a too drying effect. Ointments, such as cocaine 5 per cent., chloretone 1 per cent., or resorcin, may be completely curative.

In cases of *kraurosis* great relief is often obtained by the use of *æstrogenic hormone* given orally as stilbæstrol or hexæstrol, 0.5 to 1 mg. daily, combined with local application of stilbæstrol ointment. Intractable cases of any origin may be treated by X-ray irradiation of the vulva.

In the treatment of *leucoplakia*, local applications are usually only helpful in the first or early second stage of the disease. In the late second stage, and certainly in the third stage, local treatment is usually ineffective. Bearing in mind the high incidence of previous leucoplakia in cases of carcinoma of the vulva, free excision of the vulva should be undertaken.

CONCLUSION

From the practitioner's point of view there can be few symptoms which are more tiresome or unsatisfactory to treat than pruritus vulvæ, but from the sufferer's point of view there is almost nothing which will earn more gratitude than the relief and cessation of irritation of the vulva.

THE PREVENTION AND TREATMENT OF PROLAPSE

By H. JORDAN MALKIN, M.D., F.R.C.S. Ed., F.R.C.O.G.

*Surgeon, Nottingham Hospital for Women; Gynaecological and Obstetric
Surgeon, City Hospital, Nottingham.*

PROLAPSE of the female genital organs is one of the most common conditions encountered in a gynaecological out-patient department. The incapacity it produces, its symptoms of urinary upset, pelvic discomfort, difficulty in locomotion, and general lassitude make one wonder whether this sequel of childbearing need really occur—for it is an earlier or later sequel of childbirth in nearly 100 per cent. of cases.

ANATOMY

To understand why it occurs, and to appreciate whether or not it need occur, it will be useful to recall the factors by which the position of the uterus, vagina and adjacent organs are normally maintained. The most important structure is the levator ani muscle, a bilateral sheet of muscle arising from the back of the pubis and side wall of the pelvis as far back as the ischial spine, and sloping down to meet and fuse with its opposite half both in front of and behind the rectum and, more posteriorly still, to obtain insertion into the side of the coccyx. It forms a diaphragm deficient only anteriorly in the midline, and through this gap pass the urethra and vagina and, more posteriorly, the rectum. It follows that contraction of this muscle will diminish its slope, and therefore raise the organs—bladder, uterus and rectum—which lie above it.

The next important structure is that part of the pelvic cellular tissue which lies above the levator ani muscle and, radiating outwards from the region of the cervix, reaches to the pelvic walls; this fascia is condensed in certain areas and forms valuable ligaments of support for the pelvic contents:—

(a) The pubo-cervical ligament passing forward from the cervix at the level of the internal os, beneath the bladder, to the back of the pubis.

(b) The transverse (Cardinal, Mackenrodt) ligaments passing from the cervix laterally in the base of the broad ligaments.

(c) The utero-sacral ligaments passing from the cervix posteriorly to be inserted into the second and third parts of the sacrum on each side of the rectum.

MECHANISM OF PROLAPSE

In the process of parturition, the foetus has to pass from above the pelvic floor, outlined above, through the gap situated anteriorly, and emerge completely from the lower side. The first stage of labour, the stage of dilatation of the cervix with comparatively little descent of the foetus, plays

little part in the production of subsequent prolapse. The second stage of labour, however, the overcoming of the resistance of the pelvic floor, entails a considerable disturbance of the normal anatomical structure to enable the hard and relatively resistant foetal head to pass through the small gap between the medial borders of the anterior portion of the levators. For this to take place, considerable stretching of the medial fibres of the levator ani muscle must occur, accompanied at times by trauma from which recovery may be only incomplete.

During this process of stretching, the levators recede before the advancing head, in a backward, outward and sideways direction, until the opening is large enough for the head to pass through. Should a tear occur, it starts in the posterior vaginal wall and may involve first those fibres of the levator which are inserted just posterior to the vagina, and secondly, those fibres just posterior to the rectum.

On the completion of labour, the stretched levators, the vagina, and the superficial perineal muscles gradually recover their tone, and the uterus, from being a bulky abdominal organ, slowly involutes until it again comes to lie below the pelvic brim; and, except for some slight permanent enlargement of the uterus and introitus, and some alteration in shape of the external os, the pelvic organs again become normal. If, however, owing to *over-stretching* of, and undue trauma to, the pelvic supports, this does not occur, the bladder and uterus are inadequately maintained, and at a lower level than normal, and then descent begins: a descent which at first may be noticed only on straining or when tired at the end of the day; over a period of months or more commonly years, the descent increases, the uterus, bladder and rectum proceed farther and farther downwards in the vaginal axis until perhaps complete procidentia, in which the uterus is entirely outside the vulva, is present.

PREVENTION

During pregnancy.—Although it is not always possible to prevent a subsequent prolapse there are certain steps which can be taken to minimize its occurrence and, conversely, certain avoidable procedures which make its occurrence more likely. When we consider how important a part the pelvic floor plays in supporting not only the contents of the pelvis itself, but indirectly those of the abdominal cavity also, it behoves us to direct our efforts to avoiding undue structural trauma and to assisting the return to normal, by all the means at our command.

During pregnancy and before the onset of labour it is important that the patient should understand something of what is involved in the process of parturition, and in particular, so far as the subject under discussion is concerned, what is the second stage of labour. She should then be instructed how to use her expulsive muscles and at the same time relax her levators, as inability to coordinate these actions will increase the resistance to delivery and consequently increase the trauma to the levator fibres, and raise the forceps rate.

During labour

It is of the utmost importance to keep the patient's confidence, to maintain her interest and strength, and to interfere only if and when interference is necessary.

Too early application of forceps.—Even to-day, only too often, owing to an unruly patient or difficult relatives, the doctor succumbs to the temptation to hasten delivery far too soon, by the application of forceps before complete dilatation of the cervix and before the second stage has begun. Now if this is attempted, one of two things happens: either the cervix is sufficiently tough not to give way, in which case the foetus, uterus, and its supports are pulled on—albeit ineffectively for delivery—or else a cervical tear, which may extend into the base of the broad ligament, occurs. In the former case all the cervical ligaments undergo undue stretching, with possibly permanent interference with their ability to assist in maintaining the pelvic viscera in position. In the latter case, should the force applied to the forceps be sufficient to pull the head through the cervix, with or without a tear, and be persisted with, the levators, the vagina and its attachments, and the perineum, are subjected to rapid, and maybe continuous, pressure, delivery being effected in a matter of minutes, instead of hours. The result to the mother is either overstretching of the tissues or, more commonly, extensive lacerations requiring meticulous and time-consuming care in suture, but too often receiving scant and ineffective attention, with imperfect apposition and healing which lead in many cases to subsequent pelvic floor weakness and prolapse. The result to the child is only too often disastrous.

Too early expulsive efforts.—It is surprising how often a patient is encouraged to bear down before the first stage is completed; this results in attempts by the abdominal muscles to push down the whole uterus and its contents, a procedure which not only is ineffective as regards accomplishing delivery, but is wearing for both the patient and for the uterine supports, which may become unnecessarily stretched in the process.

Prolonged second stage of labour.—The practice of allowing a patient to remain over-long in the second stage with very slow advance, or even none at all, has little to recommend it; the continuous pressure on the pelvic floor will, by increasing the trauma, retard and perhaps prevent a return of the stretched tissues to normal, and will leave a strong predisposition to prolapse. It is quite certain that a procedure much preferable to a prolonged second stage is the application of forceps with an adequate episiotomy, followed by efficient perineal repair.

Adequate episiotomy.—This is a prophylactic procedure of great value; it is important, however, to stress the adequacy and also the direction of the episiotomy. The best results are obtained by a midline incision which can be tailed off to one or other side of the anus if necessary; should a deep one be required, the levator fibres are not cut obliquely, subsequent approximation is not difficult, and healing is satisfactory. A deliberate episiotomy followed

by accurate repair is far better for the mother than is the long, exhausting labour accompanied by prolonged stretching, which is sometimes encouraged with the object of avoiding a tear, and so producing that feeling of pride which some accoucheurs experience if no sutures have to be inserted.

Accurate perineal repair.—Perineal repair is a much abused operation. Too often inadequate skin approximation is all that is attempted. If it is appreciated that the skin is the last and least important structure to give way, it will be understood that failure to approximate the deeper tissues will leave the patient with a weak pelvic floor and potential prolapse. In this operation it is essential to have a good view of the area to be repaired; this is obtained more satisfactorily in the dorsal position than in the left lateral. If the patient is already under general anæsthesia, this should be continued; but if not, local anæsthesia (1 per cent. procaine, which is a most useful addition to the obstetrician's equipment) is very effective: the hypodermic needle should be inserted from the raw area upwards to the under-surface of the perineal skin and vaginal mucosa. The latter should be repaired first, the levators being approximated next—in each case, catgut sutures being used—and finally, the perineal skin should be united, catgut, silkworm gut or nylon sutures being employed.

The puerperium

In the puerperium the return to normal gradually takes place and much may be done to assist in the process.

Early exercises.—Help of the greatest value can be given by early exercises: general, to maintain the muscle tone of the limbs; abdominal, to counteract the stretching occurring in the later months of pregnancy; and pelvic, to restore the traumatized levators. These exercises should be given by a masseuse with special knowledge of this type of work, who can ensure that they are adequately carried out; they can be begun on the second day in the normal case, although it is advisable to wait until the fourth or fifth day if any extensive perineal repair has had to be undertaken.

Prevention of retroversion.—The normal position of the uterus is one of anteversion. It is maintained in this position by the utero-sacral ligaments which pull the cervix backwards, and the round ligaments, which pull the fundus forwards. These two ligaments acting at a mechanical advantage form a sling; any pressure on the uterus from above tends to increase the anteversion and to push the cervix backwards on to the levators, where, normally, adequate support is obtained. In the position of retroversion, however, the ligaments are overstretched and inefficient and are working at a mechanical disadvantage; moreover, the axis of the uterus is in line with the axis of the vagina, and pressure applied to it from above tends to make it slide downwards and forwards through the gap in the levators anteriorly, along the axis of the vagina. It will be appreciated therefore how important it is to ensure that the uterus involutes in the anteverted position. This can be assisted by encouraging the patient to lie in the prone position during a portion of each day after the fifth (the uterus being too large to retrovert

before this), by appropriate exercises on "all fours" when the ambulatory stage is reached and, if retroversion occurs in spite of these precautions, by reposition and insertion of a Hodge type of pessary for six weeks.

Adequate rest in bed.—Early ambulation is very much in vogue at the present time, both after operations and after confinements, patients being encouraged to get out of bed within a few days. This practice, which was popular in some countries many years ago, received new attention in this country during the air raids, when it was obviously important to everyone in hospital, not least to the patient herself, to be active and able to move to a shelter, should this be necessary. The vogue has continued, partly because of the necessity to get the patient back to normal life early, owing to lack of domestic help, and partly because of the probable decrease in the incidence of femoral thrombosis as a result of such early active movements. Whilst it seems reasonable to adopt this course after many operative procedures, including Cæsarean section, it must be borne in mind that the assumption of the erect posture, with a heavy puerperal uterus, is placing a strain on the incompletely involuted levators and cervical ligaments which they may not be able satisfactorily to bear. I cannot help feeling that early ambulation can be overdone in the case of the puerperal patient and that an increase can be anticipated in the incidence of prolapse, already high in those who for economic reasons returned to full work too early, which may soon cause a swing of the pendulum once more towards adequate rest in bed—particularly for those patients for whom ambulation means full domestic duties with no halfway house.

There remains a group of patients in whom involution is retarded and who shortly after getting up notice a feeling of pelvic discomfort and perhaps stress incontinence, and are found to have poor levator tone and general laxity. These patients are considerably benefited by wearing a ring pessary for a time, to give additional support until such time as involution is complete; after six weeks the ring can be removed and it will then be found that the patient is symptom-free.

TREATMENT

The treatment of established prolapse depends upon its degree and the severity of its symptoms. It is a well-known fact that often the degree of descent and the amount of resultant disability by no means run parallel: it is relatively common to find an extreme degree of descent, sometimes amounting to complete procidentia, which has been present for years with little disturbance to the patient, whereas in another case slight laxity of the anterior vaginal wall is sufficient to interfere with the normal bladder mechanism and produce stress incontinence, urgency or frequency, so that the patient's social activities and outdoor life are considerably interfered with.

The lines of treatment available range from improvement in the general health and levator tone in mild cases to extensive operative measures of various types for more severe cases, with a certain number of patients with

by accurate repair is far better for the mother than is the long, exhausting labour accompanied by prolonged stretching, which is sometimes encouraged with the object of avoiding a tear, and so producing that feeling of pride which some accoucheurs experience if no sutures have to be inserted.

Accurate perineal repair.—Perineal repair is a much abused operation. Too often inadequate skin approximation is all that is attempted. If it is appreciated that the skin is the last and least important structure to give way, it will be understood that failure to approximate the deeper tissues will leave the patient with a weak pelvic floor and potential prolapse. In this operation it is essential to have a good view of the area to be repaired; this is obtained more satisfactorily in the dorsal position than in the left lateral. If the patient is already under general anæsthesia, this should be continued; but if not, local anæsthesia (1 per cent. procaine, which is a most useful addition to the obstetrician's equipment) is very effective: the hypodermic needle should be inserted from the raw area upwards to the under-surface of the perineal skin and vaginal mucosa. The latter should be repaired first, the levators being approximated next—in each case, catgut sutures being used—and finally, the perineal skin should be united, catgut, silkworm gut or nylon sutures being employed.

The puerperium

In the puerperium the return to normal gradually takes place and much may be done to assist in the process.

Early exercises.—Help of the greatest value can be given by early exercises: general, to maintain the muscle tone of the limbs; abdominal, to counteract the stretching occurring in the later months of pregnancy; and pelvic, to restore the traumatized levators. These exercises should be given by a masseuse with special knowledge of this type of work, who can ensure that they are adequately carried out; they can be begun on the second day in the normal case, although it is advisable to wait until the fourth or fifth day if any extensive perineal repair has had to be undertaken.

Prevention of retroversion.—The normal position of the uterus is one of anteversion. It is maintained in this position by the utero-sacral ligaments which pull the cervix backwards, and the round ligaments, which pull the fundus forwards. These two ligaments acting at a mechanical advantage form a sling; any pressure on the uterus from above tends to increase the anteversion and to push the cervix backwards on to the levators, where, normally, adequate support is obtained. In the position of retroversion, however, the ligaments are overstretched and inefficient and are working at a mechanical disadvantage; moreover, the axis of the uterus is in line with the axis of the vagina, and pressure applied to it from above tends to make it slide downwards and forwards through the gap in the levators anteriorly, along the axis of the vagina. It will be appreciated therefore how important it is to ensure that the uterus involutes in the anteverted position. This can be assisted by encouraging the patient to lie in the prone position during a portion of each day after the fifth (the uterus being too large to retrovert

structures; this it failed to do, and the return of symptoms after a short time led to the operation being abandoned.

Modern operations are now directed to repair of the damaged and displaced tissues—the levators and cervical ligaments. Various procedures have been devised for this purpose, the most favoured one and that giving the most uniformly satisfactory results being the “Manchester” or “Fothergill” type of *pelvic floor repair*. This operation, first carried out by Donald of Manchester and elaborated by Fothergill, consists in:—

- (1) Removal of a triangle, base upwards, of redundant mucosa of the anterior vaginal wall.
- (2) Identification and suture of the pubo-cervical fascia to elevate and support the bladder base.
- (3) Amputation of the cervix and, during its reconstitution, suture of the transverse cervical ligaments in front of it so as to push the cervix backwards and upwards.
- (4) Repair of the cut edges of mucosa.
- (5) Posterior colpoperineorrhaphy, in which through a triangle, base downwards in the posterior wall, the levators are united by suture between the vagina in front and the rectum behind, suture of the mucosa and of the perineal skin then restoring the perineal body.

This operation is usually a highly satisfactory one, in that it restores the organs to their normal position and supplies adequate support to keep them there. In general, no more need be done; there are, however, many advocates of the combined vaginal hysterectomy and pelvic floor repair operation, particularly in cases of complete procidentia, and most people would agree that in the presence of any uterine symptom, such as excessive loss at or near the menopause, such a procedure is the operation of choice. That it should be done more or less routinely in the postmenopausal patient with marked prolapse is a matter about which opinions vary.

There are various other operations performed, each having its advocates in particular cases; the Manchester type, however, gives excellent results and is deservedly popular. But even this operation does not always cure the troublesome symptom of stress incontinence of urine; for this symptom, if persistent after a repeat procedure of a similar type, other operations have been devised and are gaining considerable favour. These operations aim at giving additional support to the bladder neck by means of a fascial sling. There are two main types, the *Aldridge operation* and the *Read-Millin operation*. The former is an abdomino-vaginal operation which combines a vaginal plastic repair with a fascial sling from the external oblique aponeurosis applied below the urethra. The latter is an abdominal operation in which fascial slings are obtained from transverse strips of the rectus sheath and aponeurosis of the external oblique; these strips are threaded through the rectus muscles, drawn through posterior to the urethra, and sutured to each other so as to form a sling supporting the bladder base. Many cases have now been treated by this type of operation, and there is no doubt that in the right case and in the hands of a competent operator, excellent results are being obtained.

intermediate degree of descent and symptoms who, should they so desire, or if some contraindication to operation be present, can be made comfortable by some form of support, such as a ring pessary.

It is perhaps not always appreciated that a number of cases in the first group, in which descent is slight but the bladder neck, on pressure from above—as in coughing—descends sufficiently to cause an uncontrolled leak of urine down the urethra, can be cured by treatment directed to improvement in the general health and levator tone; this entails a course of remedial exercises for the pelvic floor as mentioned earlier in this article, combined if necessary with faradic stimulation.

In more severe cases or those not responding to the above measures, additional support is required. This can be supplied either by mechanical means, the usual method being by insertion of some form of pessary, a rubber-covered watch-spring type of ring being the most popular, or by operation, by which the overstretched and displaced pelvic ligaments and muscles are restored to their normal position and maintained there by suture until healing is complete.

Pessary treatment.—The ring method, widely used before the advent of a satisfactory operative procedure, produces its results by forming a diaphragm below the uterus and bladder and above the levator ani muscles, which so long as the ring is in position is able to maintain the pelvic contents more or less in their normal position and so relieve the patient's symptoms. It is suitable as a temporary measure in those cases of pregnancy complicated by prolapse in which symptoms of descent appear only when aggravated by pregnancy. It is also indicated, as mentioned earlier, when additional temporary support is required for incipient prolapse in the puerperium. It has, however, many disadvantages: unless the levator tone is good and there is little undue separation of its free borders it may be found that the ring will not stay in position, in which case it does not cure the symptoms and tends to be expelled on exertion, such as coughing or defæcation. Further, it requires regular changing, cleaning and replacement, in spite of which it may cause vaginal and cervical infection leading to persistent and unpleasant leucorrhœa. Nevertheless, in a suitable case, one in which operative measures are contraindicated or when it is impossible to take the necessary time off from domestic or other duties, pessary treatment plays an important part in the relief of symptoms. It will be appreciated, however, that for an established prolapse, pessary treatment cannot provide a cure, and that symptoms will gradually return on its removal.

OPERATIVE TREATMENT

Various operative procedures have been devised to restore the pelvic viscera to their normal position. It is understandable that in the earlier days attempts were made to maintain the correct position by suturing the uterus to the abdominal wall in the hope that this would also keep up the adjacent

dition which is not fully understood and the treatment of which is still empiric. Moreover, there is some evidence, admittedly of a tenuous nature, that manipulation of the cervix may influence the anterior pituitary. Assuming what now is loosely termed a psychosomatic relationship in gynæcological disorders, it is reasonable to expect peripheral stimuli to affect the centre, and it can be noted in passing that dilatation of the cervix alters the electro-encephalographic tracing.

DIAGNOSTIC USES

A dilatation and curettage must be done in the presence of *postmenopausal bleeding*, as in about half of the patients who have this symptom it arises from malignant disease of the cervix or uterine body. Besides establishing or disproving this diagnosis other pathological lesions may be demonstrated, and so appropriate treatment may be instituted (e.g., senile endometritis). Curetting is also essential in *irregular or intermittent genital bleeding* during adult life in women. Here again, malignant disease may have to be considered: alternatively it will be necessary to define such typical endometrial lesions as metropathia hæmorrhagica, which will enable proper treatment to be undertaken. Curetting must also be done for diagnostic purposes in any patient in whom the production of an artificial menopause is contemplated.

The need for curetting in *true menorrhagia* may be less than in metrorrhagia because the cause may be more easily diagnosed by pelvic examination (e.g. fibroids), or may be due to more general disorders. However, a small fibroid may be felt by the sound or finger more easily than may a slight enlargement of the uterus be detected by palpation.

Modern investigation of *infertility* includes in its routine an attempt to assess ovulation as judged by defining a phase of progesterone activity in a small piece of endometrium removed at the time when insufflation of the Fallopian tubes is undertaken. This involves curetting, although only to a very limited extent.

THERAPEUTIC USES

Dilatation and curettage provides a simple and effective cure in cases of *incomplete abortion* when bleeding may be continuous and profuse even from small septic portions of retained products. Whilst the indication for interference is hæmorrhage, it must be remembered that there may be coincident infection. Therefore unless the indication for interference is of urgency, it is wise to establish a diagnosis of infection if present, and to control it first by sulphonamides and penicillin, if necessary. Occasionally, a "D. and C." may have to be done when *therapeutic abortion* is indicated. It is now realized, since the pathology of pregnancy has been taken more seriously, that the indications for termination of a pregnancy are more sharply defined: for example, it is, or should be, uncommon to terminate

THE PRESENT STATUS OF DILATATION AND CURETTAGE

By KENNETH BOWES, M.D., M.S., F.R.C.S.

Obstetric Physician, St. Thomas's Hospital.

"THE feasibility of an operation or the completeness with which it can be done is not the best indication for resorting to it". This dictum of Sir Henry Cohen on the subject of surgery in general can be applied with particular aptitude to the most simple operation of gynæcology—dilatation and curettage ("D. and C."). Formerly, excessive use of this operation may have been excusable, but to-day its limits are much more sharply defined owing to the increase in knowledge of gynæcological pathology, and the realization that many disorders of function are merely reflected in the endometrium, whilst the cause lies in the hormonal system of the ovary, anterior pituitary, and other glands. Moreover, since Randall introduced the small strip curette in 1935, it has been possible to perform a sampling "endometrial biopsy", as it is now termed, rather than a full-scale dilatation and curettage in the case in which only a small piece of endometrium is needed to establish a diagnosis. A further reason for dilatation and curettage being performed less frequently is the realization that it is uncommon for a vaginal discharge to originate from the endometrium. Thus, no longer should the uterine mucosa be disturbed by unnecessary curetting. More modern methods of cauterization of the cervical glands can be applied topically.

It is well to define what may properly be accomplished by performing a dilatation and curettage. First, diagnosis; particularly in cases of uterine hæmorrhage. The operation here is an essential step in the investigation of bleeding from the genital tract following the menopause. A "D. and C." permits of examination of the endometrium, of removal of polypi and, if necessary, of palpation by the finger or sound of the topography of the endometrial cavity. Secondly, by the removal of pathological material curetting may cure some cases of uterine bleeding (incomplete abortion, foreign bodies). Thirdly, dilatation of the cervix alone gives access to the cervical canal so that it can be examined for a cervical polyp or growth which previously may not be visible. It is also a necessary preliminary to efficient cauterization of the cervix by any method. Fourthly, there remains the possibility of an empiric function of dilatation and curettage. The scope of this rôle has been much reduced since endometrial pathology has been better understood. Assuming that "X" the unknown quantity can be applied to clinical medicine, there must still be room for empiricism. Dilatation of the cervix is thus useful in spasmodic dysmenorrhœa, a con-

dition which is not fully understood and the treatment of which is still empiric. Moreover, there is some evidence, admittedly of a tenuous nature, that manipulation of the cervix may influence the anterior pituitary. Assuming what now is loosely termed a psychosomatic relationship in gynaecological disorders, it is reasonable to expect peripheral stimuli to affect the centre, and it can be noted in passing that dilatation of the cervix alters the electro-encephalographic tracing.

DIAGNOSTIC USES

A dilatation and curettage must be done in the presence of *postmenopausal bleeding*, as in about half of the patients who have this symptom it arises from malignant disease of the cervix or uterine body. Besides establishing or disproving this diagnosis other pathological lesions may be demonstrated, and so appropriate treatment may be instituted (e.g., senile endometritis). Curetting is also essential in *irregular* or *intermittent genital bleeding* during adult life in women. Here again, malignant disease may have to be considered: alternatively it will be necessary to define such typical endometrial lesions as metropathia hæmorrhagica, which will enable proper treatment to be undertaken. Curetting must also be done for diagnostic purposes in any patient in whom the production of an artificial menopause is contemplated.

The need for curetting in *true menorrhagia* may be less than in metrorrhagia because the cause may be more easily diagnosed by pelvic examination (e.g. fibroids), or may be due to more general disorders. However, a small fibroid may be felt by the sound or finger more easily than may a slight enlargement of the uterus be detected by palpation.

Modern investigation of *infertility* includes in its routine an attempt to assess ovulation as judged by defining a phase of progesterone activity in a small piece of endometrium removed at the time when insufflation of the Fallopian tubes is undertaken. This involves curetting, although only to a very limited extent.

THERAPEUTIC USES

Dilatation and curettage provides a simple and effective cure in cases of *incomplete abortion* when bleeding may be continuous and profuse even from small septic portions of retained products. Whilst the indication for interference is hæmorrhage, it must be remembered that there may be coincident infection. Therefore unless the indication for interference is of urgency, it is wise to establish a diagnosis of infection if present, and to control it first by sulphonamides and penicillin, if necessary. Occasionally, a "D. and C." may have to be done when *therapeutic abortion* is indicated. It is now realized, since the pathology of pregnancy has been taken more seriously, that the indications for termination of a pregnancy are more sharply defined: for example, it is, or should be, uncommon to terminate

pregnancy in the tuberculous patient. The correct use of dilatation and curettage in these cases of termination will depend upon the stage of pregnancy and whether or not sterilization should be done at the same time.

Dilatation and curettage may also have a function in arresting temporarily hæmorrhage in a condition such as *metropathia hæmorrhagica* and thus allowing for the condition of the patient to be improved while appropriate other treatment is applied.

Lesions of the cervix.—The realization that leucorrhœa originates from cervical or vaginal infections, and the construction of modern cauterizing apparatus of electric or diathermy strip types, have led to effective therapy by these means. For their application dilatation of the cervix is a necessary preliminary. It is also wise to dilate before removing cervical polypi; unless these are removed to their bases recurrences will take place.

Dilatation of the cervix still retains its position in the treatment of *spasmodic dysmenorrhœa*, although only about a quarter of patients will be relieved completely. It is not usually necessary or desirable to follow the dilatation by curettage.

CONDUCT OF THE OPERATION

The steps of this small procedure are so well known that it is necessary only to mention some points of importance. Curetting is best performed during the third week of the menstrual cycle if the patient is of adult age and has a normal 28-day cycle, so as to assess the ovarian function from the curettings. Careful note should always be made of the patient's last normal menstrual period preceding the operation.

Although a trivial operation, it must be remembered that the uterine body is related anatomically to the peritoneal cavity. Perforation of the uterus, though usually not followed by untoward event, can be dangerous. Moreover, the symptom of bleeding may be merely the outward and visible sign of an inward pelvic infective process. The association of any form of tubal infection can be disastrous if curetting is performed. For this reason, as also for the fact that an early pregnancy may be present, it is most important for full examination to be performed under anæsthesia before proceeding with curetting. It is surprising how often the findings at this examination are found to differ from those recorded previously in the patient's notes. Here, too, may be emphasized the importance of adequate relaxation by anæsthesia to make the examiner's task an easy and accurate one.

In the *aged patient* the combination of a uterine wall which can be perforated easily, together with the possibility of pus in the cavity (pyometra), should be anticipated. The senile uterus is more easily perforated than is the pregnant one, and the pus in a pyometra, although not yielding organisms of a gross virulence, is capable of giving rise to serious peritonitis.

To carry out the operation small toothed volsella should be used to hold the cervix. Others with large teeth can easily avulse portions of the cervix

if pressure has to be used to dilate the canal. The traditional sound should be passed to assess the uterine cavity in shape, size and position. Uterine dilators may pass more easily if lubricated with dettol cream. Dilatation to size 9 or 10 is enough for curetting, and to size 14 in cases of dysmenorrhœa. Simple systematic curetting is then performed. If retained products of any bulk have to be removed, or if an ovum is being extracted, ovum forceps are necessary, and the products should be removed by first twisting the mass round and then gently extracting it. Digital exploration is preferable to the curette.

Following a curettage the products should be examined carefully, first by the naked eye aided by a lens, and later by the microscope. If several cases of a similar nature are being operated on following each other, it is important that the curettings should be attributed to the appropriate patient. Labelling must therefore be carried out carefully.

In cases in which only a small strip of endometrium is needed for diagnosis of the state of the endometrium in relation to its response to hormones, or in which a putative diagnosis of ovulation arises, the full-scale curettage is not necessary. In these cases (endometrial biopsy) a small strip-sampling curette may be used. This removes a portion of endometrium on stroking the curette down on withdrawing it from the uterus. In many cases anæsthesia is not necessary, as the instrument is of small calibre and can pass through the undilated cervical canal. The procedure can be carried out in a properly equipped out-patient department, the patient experiencing little discomfort. Several types of these curettes are available, the simplest being based on Randall's.

SOME DIFFICULTIES IN DILATATION OF THE CERVIX

Occasionally it may be difficult to find the cervical canal. Some cervixes will only admit a probe and a passage has to be sought, as in dilating a urethral stricture. Once the canal has been identified the usual uterine dilators can follow.

The conical cervix with a small external os should be dilated with care, or it may split. Sometimes it is better to use an old-fashioned laminaria tent to dilate the os slowly before using instruments.

In the pregnant uterus a tear of the cervix may lead to marked bleeding if it extends laterally towards the region of the uterine artery.

COMPLICATIONS

These are: perforation of the uterus, hæmorrhage, and infection.

Perforation probably occurs more frequently than is appreciated. Although it is disconcerting to the operator to see the sound or dilator pass freely for a distance which indicates perforation, provided that no further interference takes place and the uterine cavity is not infected, there may be no sequelæ.

The patient should be sent back to the ward and a pulse chart kept. If there is any fear of infection it is wise to use sulphonamides and penicillin prophylactically. Perforation can be dangerous if not recognized, and if it occurs in the pregnant uterus or in an old patient with a pyometra. In the former the embarrassing situation can arise whereby abdominal viscera are delivered by the ovum forceps. In these cases it will be necessary to perform laparotomy as, quite apart from any other reason, the mesenteric blood supply to the intestine may have been affected.

If the uterus is perforated in the presence of a pyometra the abdomen should be opened, the uterus removed, and chemotherapy established.

Hæmorrhage.—Marked bleeding can occur if the cervix splits and the tear extends to one or other broad ligament. Stitching the tear with mattress sutures will usually control the bleeding. If it occurs in less degree the canal may be plugged with gauze soaked in an antiseptic.

Infection may be produced by lighting up a dormant infection, by perforation of the uterus, or by introducing organisms at the time of operation. The last, of course, should not happen. Infection takes a few days to establish itself and there may be no apparent cause for alarm for two to three days; then the temperature rises steeply and various signs of peritonitis become evident. It is best to be wise before the event by eliminating from this operation patients who have signs of salpingitis, and by giving treatment prophylactically to any patient in whom perforation has occurred and in whom there is any doubt as to the question of infection. In cases of established infection general nursing and surgical principles apply.

In passing, it is worthy of note that minor degrees of infection may easily be caused by dilatation and curettage. The normal vagina and uterus are well protected from infection by the physiologically protective bacterial flora of the vagina and by the barrier of the cervix. Operation may, however, disturb this relationship and may aid infection by introducing organisms, and by providing blood clot and dead tissue for their nutrition. It is possible therefore for a patient to have a resulting mild infection and vaginal discharge produced by this minor operation.

After-care.—The modern trend to early rising should be encouraged.

THE TREATMENT OF "ATHLETE'S FOOT"

By G. B. MITCHELL-HEGGS, O.B.E., M.D., F.R.C.P.

Physician in charge of Skin Department, St. Mary's Hospital; Physician, St. John's Hospital for Diseases of the Skin.

ATHLETE's foot is a chronic relapsing condition affecting the skin of the foot, particularly the soft, moist areas between the toes. The symptoms are well known, as the disease, in its less severe forms at least, is a very common complaint. Itching, desquamating layers of sodden white skin, and the appearance of deep painful cracks between the toes are the usual early manifestations. Later the affection may spread to the sole and dorsum of the foot, as a red, scaling area, or groups of vesicles may arise on the instep, apparently *de novo*. For months the patient may have little or no trouble with his feet, only to suffer a recrudescence of symptoms in hot weather, or when the feet have become hot and sweaty. This may occur when the patient is confined to bed on account of some other disease, or after a long walk.

In a large proportion of cases the cause of the condition is a fungus infection of the skin. Synonyms for this infection are *tinea pedis*, *epidermophytosis*, *dermatophytosis* and *dermatomycosis*. The fungus can be demonstrated by direct microscopy or identified in culture. Both the *epidermophyton* and the *trichophyton* occur in *tinea pedis*. Sodden, whitish skin between and beneath all the toes is generally due to a yeast, *Monilia albicans*. The remaining cases of what the laity diagnose as "athlete's foot" are due to other causes, including bacterial infection, and the internal and external factors of eczematous dermatitis.

DIAGNOSIS

BEFORE instituting treatment it is of paramount importance to be sure of the diagnosis, as fungicides applied to eczematous or septic, bacterially infected lesions are more likely to exacerbate than to improve them. Diseases commonly mistaken for "athlete's foot" are intertrigo, with maceration produced by stale sweat often becoming secondarily infected by pyogenic cocci or by monilia; dermatitis due to antiseptics or fungicides; dermatitis due to some substance in the socks or shoe leather; pompholyx secondary to general metabolic or psychosomatic disorder; and pustular psoriasis or pustular bacterides. In some cases the fungus infection appears to have been treated successfully by the patient, but the skin has been left in an eczematous condition as a result of the application of the fungicide, and is then made worse by further unnecessary treatment.

The diagnosis can only be made with complete certainty by demonstrating the fungus microscopically in the skin taken from the edge of the spreading lesion, or by growing it on Sabouraud's proof agar.

Skin found just beyond the outer limits of peeling, or that covering the vesicles

in the same area, is the most likely to give positive results. It should be removed and soaked in 25 to 30 per cent. potassium hydroxide for from a half to one-and-a-half hours, applied to a slide and examined microscopically. No staining is necessary; the mycelial threads will be seen branching in the epithelium if the skin is sufficiently macerated by soaking for this period, which allows time for the scales to become transparent. The process can be assisted by gentle application of heat for a few minutes and separation of the cells by teasing with the point of a needle.

The technique used by Mr. Symms in the laboratory of St. John's Hospital for Diseases of the Skin is as above, and has been found to produce rapid clearing of the specimen. It should, however, be remembered that soaking for as long as six to twelve hours may be necessary for examination of specimens taken from the nail.

If these methods are impracticable, a careful examination should be made of the spreading edge of the lesion. If a fungus infection is present, the reddest part of the patch will be at the edge, the free margin of loose skin will face centrally, and immediately beyond the edge tiny vesicles will be seen, deeply placed in the epidermis. Flexures such as the groins, natal cleft, and the axillæ should also be examined at the same time to detect spread of the infection from one part of the body to another.

The fungus may spread by direct infection or, in certain circumstances, by the blood stream. It may, however, be responsible for a symmetrical vesicular eruption of the hands, clinically indistinguishable from cheiropompholyx, indicating that a state of allergy has arisen. This is called an "ide" eruption. The epidermal cells in this area have become allergic, or unusually sensitive, to a substance produced in the skin by the fungus affecting the feet. These sensitized cells are also sometimes unduly sensitive to sunlight—photophytosensitization. Such an eczematous eruption, whether it starts on the feet, between the fingers or even on the face, may rapidly involve the whole body. No fungus is found in these vesicles, and fungicides are not indicated; symptomatic treatment only is required while the primary lesion receives fungicides.

A fungus in spore form may be responsible for a silent infection of the thick skin of the soles of the feet, as well as the loose skin around the nail folds or the specialized horn or keratin substance of the nail itself, and it is not uncommon to find that patients have had brittle, discoloured nails due to fungus infection for many years before they are troubled by the manifestations of "athlete's foot". In hot, moist climates the fungus infection remains in footwear, particularly the inner soles of boots and shoes, and can be cultivated if these are incubated. The skin infected by fungi or yeast is vulnerable to bacterial infection, leading to localized pyoderma, erysipelas, cellulitis, or lymphangitis and, if prolonged or recurrent, may even lead to elephantiasis as a result of chronic fibrosis with blockage of the lymph channels. Enlargement with pain and tenderness of the lymph glands in the groin is not uncommon in cases in which secondary infection is present. The pain and œdema of the foot or ankle, and stiffness of the limb, often lead to abnormalities of gait. Lumbago and sciatica may follow.

TREATMENT OF FUNGUS INFECTION

Fungus infection is widely prevalent, and it is unlikely that anyone can at all times avoid exposure to it. The natural condition of the feet appears to be the deciding factor whether or not infection results, any degree of hyperhidrosis making it likely to occur. The fungus does not take root in dry feet, where the skin never reaches the macerated condition favourable to its implantation and survival. On the other hand, freely flowing perspiration which evaporates immediately is not conducive to its growth; it is in fact a deterrent. It is in the enclosed areas where evaporation is impeded that the fungus flourishes. Freshly secreted perspiration is on the acid side, due to the presence of fatty acids, and these discourage the growth and survival of fungi; on prolonged contact with the skin the fatty acids volatilize or form salts, the stale secretion becomes alkaline and forms an ideal culture medium for fungi.

These facts should be borne in mind in the prophylaxis and treatment of the disease. Hot climates are unfavourable, particularly if thick socks and heavy boots are worn; the ideal footwear to keep the skin dry and inimical to fungi is an open-toed sandal. Prolonged standing, leading to stasis in the venous return from the foot, varicose veins, and vasomotor disorders affecting the lower limb, may occasionally be contributory factors. Anxiety states, associated with moist sweaty hands and feet, play a part in some cases. Footwear should be comfortable, as ill-fitting shoes may aggravate hyperhidrosis and friction dermatitis. Socks and stockings should not be tight, as squeezing the toes together encourages the development of moist intertriginous friction dermatitis between the toes. Rubber boots which prevent evaporation should be avoided; many people even find that their feet are more sweaty when they wear rubber-soled boots or shoes. The feet should be washed frequently and dusted with powder to absorb moisture. Warm water may be best to cleanse the skin, but a few minutes in really cold water has a good hardening effect. It is not necessarily an advantage to use antiseptic powders; ordinary dusting powders are usually satisfactory, and are unlikely to initiate sensitization.

Prevention of recurrence.—It is not difficult to bring about a remission of symptoms, but to effect a complete cure and freedom from recurrence is far from easy. The reason for this is that the skin has a natural hyperkeratotic reaction to invasion by fungus, and these hyperkeratotic layers of epidermis form a protection to the spores, enabling them to resist treatment. The nail folds also form sheltered crannies in which the spores can lurk. Recurrence is believed to be due more often to reactivation of these dormant spores than to reinfection from outside. Reinfection does occur, however, and sterilization of the patient's own socks and shoes must not be overlooked. Cotton socks should be boiled; those made of materials or mixtures which cannot be boiled should be soaked in a disinfectant before washing; 3 per cent. formalin in water is satisfactory. Shoes can be swabbed-out with the same solution, or 20 per cent. dettol, or can be left in an airtight box

in which formalin has been placed, for several days. It is wise to remember, however, that formalin itself may lead to dermatitis in patients who have a skin that is easily irritated.

Fungicides.—There are many satisfactory fungicides, and many vehicles in which they may be applied. Salicylic acid is sometimes added to a preparation as a keratolytic, in strengths over 3 per cent., to expose spores protected from the fungicide by keratin: in strengths below 3 per cent. it is a keratoplastic. In fact it has been shown that salicylic acid increases the efficacy of many fungicides. Treatment may be applied in the form of baths, powders, ointments, pastes and paints. The first two methods are chiefly symptomatic or prophylactic, but a thorough soak in hypertonic saline, coloured pink by the addition of potassium permanganate, 1 : 5000, is a good initial treatment. It ensures that dirt, sweat and many bacteria will be cleansed from the skin. When actual fungus infection is present, the choice should be made from the latter three, depending upon the condition of the skin. If it is dry and cracked, ointments will soften it; if it is boggy and moist, paints will help to dry it up. In the acute stages, if copious exudation is present, pastes are the most useful. Often a combination is best, such as ointment at night, with socks in bed to keep it from being wiped off on the sheets, and a paint by day. Since most paints contain a percentage of alcohol they should not be prescribed when deep cracks are present, as they can cause great pain. One or two applications of tincture of benzoin are, however, often effective and justify a short-lived pain.

The active principles employed in treatment fall into two main groups: the chemical fungicides, which include benzoic acid, iodine, antiseptic dyes, dithranol and chrysarobin, and the natural fungicides, fatty acids which are found in freshly secreted sweat. Much work has been done recently in America on this latter group, and many fatty acids, as well as their salts and esters, have been tested. So far no agreement has been reached as to which substance is the most effective, but among the most popular are salts of undecylenic acid, propionic and caprylic acids in conjunction, and the ester glycol dipropionate. The fungicidal action of these acids is possibly no greater than old-established treatments, but there is less likelihood of causing irritation of the skin and secondary eczematous reaction. The following are suitable strengths in which to use the different medicaments mentioned:—

Powders

- | | |
|--|----------|
| (1) Sodium hexametaphosphate (to diminish hyperhidrosis) | 5.0 |
| Salicylic acid | 2.0 |
| Zinc oxide | 31.0 |
| Boric acid | 31.0 |
| Talc powder | to 100.0 |
| (2) Zinc undecylenate | 20.0 |
| Talc powder | to 100.0 |

The number of proprietary preparations recommended for use in this

disorder are legion, so a few only can be mentioned. Occasionally, patients may use a fungicidal preparation long after the fungus is destroyed and in the end encourage the development of a sensitization dermatitis. In these cases it is helpful to know the exact formulæ of the preparations used, in order to avoid using a similar one again and thus aggravating the picture. It is sometimes a good plan to use a sedative powder for a few days, and the following can be recommended:—

(1) Desitin powder, or morrhulin.

(2) Ichthammol powder (Fissan) or Fullers' earth powder (Cimolite: Taylor).

Ointments

(a) Modified Whitfield's:—

Benzoic acid 10 per cent.

Salicylic acid 6 per cent.

In Halden's emulsifying base simplex.

(b) Undecylenic acid, 5 per cent., in emulsifying base.

(c) Sodium propionate, 25 per cent., in ointment (a).

Among the numerous proprietary preparations, the effective ones include:—

Mycozol (Parke Davis)

Chlorotone 5 per cent.

Salicylic acid 4 per cent.

Mercuric salicylate 4 per cent.

In an ointment base..... to 100

(This preparation is made in both liquid and powder forms.)

Tineafax (Burroughs Wellcome & Co.)

Zinc undecylenate 8.0

Zinc naphthelate 8.0

Mesulphen 8.0

Methyl salicylate 2.5

Terpineol 2.5

Phenyl mercuric acetate 0.06

Ointment base 70.94

(There is a powder with similar ingredients.)

Mycil (British Drug Houses)

Ointment: *p*-chlorophenyl-*a*-glycerol ether 0.5

Water-miscible base..... to 100.0

Powder: *p*-chlorophenyl-*a*-glycerol ether 1.0

Talc, zinc oxide, boric acid, starch to 100.0

Phytodermine (May and Baker)

Cream: Phenyl mercuric acetate 0.167

Salicylic acid 3.0

Terpineol 1.0

In an emulsion ointment base..... to 100.0

Powder: Methyl *p*-hydroxybenzoate 5.0

Salicylic acid..... 5.0

Talc 90.0

Mycoclen (Bencard)

Ethyl ester of hydroxybenzoic acid 5.0

O/Hydroxybenzoic acid 2.0

Methylated spirit 93.0

in which formalin has been placed, for several days. It is wise to remember, however, that formalin itself may lead to dermatitis in patients who have a skin that is easily irritated.

Fungicides.—There are many satisfactory fungicides, and many vehicles in which they may be applied. Salicylic acid is sometimes added to a preparation as a keratolytic, in strengths over 3 per cent., to expose spores protected from the fungicide by keratin: in strengths below 3 per cent. it is a keratoplastic. In fact it has been shown that salicylic acid increases the efficacy of many fungicides. Treatment may be applied in the form of baths, powders, ointments, pastes and paints. The first two methods are chiefly symptomatic or prophylactic, but a thorough soak in hypertonic saline, coloured pink by the addition of potassium permanganate, 1 : 5000, is a good initial treatment. It ensures that dirt, sweat and many bacteria will be cleansed from the skin. When actual fungus infection is present, the choice should be made from the latter three, depending upon the condition of the skin. If it is dry and cracked, ointments will soften it; if it is boggy and moist, paints will help to dry it up. In the acute stages, if copious exudation is present, pastes are the most useful. Often a combination is best, such as ointment at night, with socks in bed to keep it from being wiped off on the sheets, and a paint by day. Since most paints contain a percentage of alcohol they should not be prescribed when deep cracks are present, as they can cause great pain. One or two applications of tincture of benzoin are, however, often effective and justify a short-lived pain.

The active principles employed in treatment fall into two main groups: the chemical fungicides, which include benzoic acid, iodine, antiseptic dyes, dithranol and chrysarobin, and the natural fungicides, fatty acids which are found in freshly secreted sweat. Much work has been done recently in America on this latter group, and many fatty acids, as well as their salts and esters, have been tested. So far no agreement has been reached as to which substance is the most effective, but among the most popular are salts of undecylenic acid, propionic and caprylic acids in conjunction, and the ester glycol dipropionate. The fungicidal action of these acids is possibly no greater than old-established treatments, but there is less likelihood of causing irritation of the skin and secondary eczematous reaction. The following are suitable strengths in which to use the different medicaments mentioned:—

Powders

(1) Sodium hexametaphosphate (to diminish hyperhidrosis)	5.0
Salicylic acid . .	2.0
Zinc oxide . .	31.0
Boracic acid	31.0
Talc powder .	to 100.0
(2) Zinc undecylenate .	20.0
Talc powder to 100.0

The number of proprietary preparations recommended for use in this

the fungus, although X-ray therapy designed to produce permanent diminution of sweating should not be given.

Dosage is a matter for consideration of the individual case by one experienced in X-ray therapy of disorders of the skin, and usually three or four doses of between 75r and 100r units will be satisfactory, at an interval of five to ten days. Filtration with $\frac{1}{2}$ mm. of aluminium and a floridity of 95 to 100 k.v. has proved satisfactory in my experience. Higher doses with longer intervals between treatments may be necessary in cases of hyperhidrosis, but overdosage or a repetition of the normal dose within eighteen months should be discouraged, and the patient should be warned of the danger of X-ray burns.

In certain circumstances, thorium varnish may be used: 500 e.s.u., four times, at weekly intervals.

Lotions and ointments containing metals are held by most to be contra-indicated in conjunction with roentgenotherapy, but there is no objection to the use of substances of high molecular weight, such as the *aniline dyes*. In a large series of Service cases treated in the Far East during the last war, J. R. Owen (personal communication) found that this combination of methods accelerated the return of the diseased skin to a more normal state. These were long-standing cases occurring under subtropical conditions which included heat with high humidity.

CONCLUSION

To summarize a good routine of treatment:—

(1) When there is no evidence of added bacterial infection:—

- (a) Clean the feet with soap and water.
- (b) Dry, especially between the toes.
- (c) Snip off dead skin with scissors, which should have been sterilized and should be sterilized again after use.
- (d) Confirm the diagnosis by examination of suitable pieces of skin for fungus infection. If fungus infection is found, other likely sites of infection, such as the armpits, groins or natal cleft, should be examined and, if necessary, treated.
- (e) Apply an appropriate fungicide in a suitable vehicle twice daily.
- (f) Socks and shoes should be cleansed, or sterilized when practicable; otherwise they should be put in a warm, dry place, particularly in sunlight, but preferably not in an oven as this will loosen the wax on the threads in the shoes.
- (g) As soon as the fungus infection is under control, it is best to stop the application of antiseptics and fungicides, and use bland powder, lotion or ointment.

(2) When there is bacterial infection it is best for the patient to be confined to bed or to the house, so that the feet may be lifted above the level of the hip and the limb rested. Appropriate local antiseptic treatment should be applied; when necessary it should be assisted by systemic chemotherapy with the sulphonamide drugs by mouth, or penicillin by intramuscular injection. As soon as the bacterial infection is under control, the patient may be allowed to walk about and plan (1) be instituted.

Aeroped (Aeroped Ltd.)

Methyl salicylate	1.0
Benzoic acid	2.0
Terpineol	1.0
Glycerin	5.0
Phenyl mercuric nitrate	0.05
In ointment base	90.0

Desenex (Wallace & Tiernan)

Zinc undecylenate	20 per cent.
Undecylenic acid	5 per cent.
In a water-miscible base	

Pedzyl (Antigen Laboratories)

Ointment: Undecylenic acid	16.3 per cent.
Triethanolamine	8.7 per cent.
Titanium oxide	2.0 per cent.
Deodorant	1.0 per cent.
In a hydrophilic base	

(The base consists of a mixture of propional and ethylene glycol polymers.)

Powder: Undecylenic acid	5.0
Purified talc	57.0
Bentonite	17.5
Zinc stearate	20.0
Deodorant	0.5

To encourage desquamation, chrysarobin and dithranol (anthrobin, derobin) are satisfactory, provided they are used only for a matter of from seven to ten days. A useful paste is: dithranol, 0.5 per cent. in Lassar's paste.

Paints.—The following are useful:—

(1) When the skin is moist and sweaty:—

(a) Castellani's carbolic fuchsin.

(b) Triple dye.

(c) Benzoic acid, 3 per cent., and salicylic acid, 3 per cent., in industrial spirit.

(d) Gentian violet, 1 per cent., brilliant green, $\frac{1}{2}$ per cent. in water, applied twice daily (Owen, personal communication).

(2) In resistant cases:—

Cignolin, 2 per cent., in benzene or chloroform.

TREATMENT WHEN FUNGUS HAS NOT BEEN DEMONSTRATED

The treatment of cases of "athlete's foot" due to causes other than fungus infection is chiefly the application of simple foot hygiene. The feet should be kept as clean and dry as possible: potassium permanganate baths are useful, and a bland ointment, such as calamine, may be needed for cases with fissures and cracks between the toes.

In chronic or recurrent cases, *X-ray therapy* must be considered. The epidermal cells, rather than the infecting organism, are treated. The decision for administration should be made by an expert dermatologist. It is possible that X-ray therapy on the skin, by diminishing the amount of sweating, alters the host-parasite relationship, and makes the skin less favourable to

normal brothers and sisters) as they like and with whom they like. The older ones naturally tend to mix together and play billiards and ping-pong; the younger ones play with building sets, wooden bricks, cars, plasticine, chinks, mosaics. Tea is made, the babies crawl about the floor and the atmosphere is most informal—and incidentally full of dust!

By observing the children in their natural environment—that of play—and by discussion with the mothers and older children an attempt is made to answer Halliday's queries concerning psychosomatic disease in general: "What sort of child is this? Why did he get the disease he did? Why did he get the disease when he did?"

The idea of this Play Clinic is not original, but was taken directly from Rogerson of Guy's, whose recent death we all so much deplore. He found in his clinic that nearly all the children showed an initial anxiety and lack of self-confidence, far greater than that usually seen. Some would scarcely play at all, and others only very cautiously with a few toys in a corner of the room. Soldiers and cannon were treated carefully and often with alarm. When the children became more confident their behaviour showed an aggressiveness and over-activity in marked contrast to their earlier play. During this phase of vigorous activity there was in most cases a striking clinical improvement, but relapses occurred if the children's freedom of self-expression was curtailed or thwarted in any way. He regarded this behaviour as typical of asthma and as expressing underlying emotional tension. Such things as over-anxiousness about school work and over-fussiness of mothers are obvious examples of situations productive of tension in a child (Rogerson, C. H. (1937): *Quart. J. Med.*, 24, 367).

We have failed to corroborate Rogerson's findings as regards the behaviour of our thirty children *at play*. They seemed on the whole to be normal. The older ones thoroughly enjoyed playing ping-pong and billiards. The quiet or shy little ones played happily with mosaics and jig-saws; the more boisterous ran about after balls and chased each other. Often, like all children, they ceased to play properly and simply "mucked about", threatening one another amicably with billiard cues and hitting the ping-pong balls wildly all over the room. It would have been quite impossible for an independent observer to pick out our asthmatics from among their normal brothers and sisters. Naturally the children vary—some are shyer than others—but do they differ as a group from normal children? We thought not, superficially, but to determine the point we asked the headmistress of a small school for a report on her fourteen healthy children. She said "one is antisocial and uncooperative; one completely home-ridden and with no desire to try anything at all difficult—mother overwhelmingly fussy and anxious; one very little go and no push, and one weeps too easily". She found them all excitable, and 100 per cent. were self-conscious, some more than others. All except the one, were cooperative in general games, obviously enjoying companionship and keen to do well at work. Our

ASTHMA IN CHILDHOOD

EXPERIENCES IN A LIVERPOOL PLAY CLINIC

By C. ASTLEY CLARKE, M.D., F.R.C.P.

*Assistant Physician, Royal Liverpool United Hospital (David Lewis
Northern Branch).*

It was Buckle who said of history that if one could know all the circumstances leading up to an event one would be able to explain exactly why that event happened.

Asthma is a way of reacting to many different, often summing stimuli. It has no one "cause" but, using Buckle's argument, *if* we were able to know the circumstances leading up to an attack we should theoretically be able to say why that attack occurred. It is as well to be humble and to realize that this is a counsel of perfection. Anyone who has run an asthma clinic for any length of time knows that in a considerable number of cases one simply ends up by saying "I do not know". But patience is sometimes rewarded and in children, so it seems to me, an assessment of that important thing, "the total situation", is more easily arrived at than in grown-ups who, as all children know, are complicated and unpredictable beings, set in their ways and ruled by the basest motives. Hence the Play Clinic.

THE PLAY CLINIC

Here asthmatic children between the ages of three and fourteen come together once a week, with or without their mothers, to report progress and to play. The Clinic has dealt with all the asthmatic children who were referred to the asthma clinic proper by their general practitioners during the course of twelve months; the group is therefore entirely unselected and the children were not referred for psychiatric reasons. At the main clinic a full history had been taken and physical examination carried out; skin tests were also done as a routine, together with X-rays of chest and sinuses and a specialist opinion on ear, nose and throat. A line of physical treatment had then been decided upon.

The *raison d'être* of the play clinic is to evaluate the results of the physical treatment, to assess the background of the child and to arrive at some sort of conclusion as to the circumstances in which the attacks are produced.

Two helpers, experienced in the problem of asthma and in looking after children, preside over what really amounts to an informal group discussion with the mothers, and extract from them all possible information relating to the attack. The children in the meantime play (often accompanied by

Read before the British Association of Allergists, April 1949.

August 1949. Vol. 163

(130)

normal brothers and sisters) as they like and with whom they like. The older ones naturally tend to mix together and play billiards and ping-pong; the younger ones play with building sets, wooden bricks, cars, plasticine, chalks, mosaics. Tea is made, the babies crawl about the floor and the atmosphere is most informal—and incidentally full of dust!

By observing the children in their natural environment—that of play—and by discussion with the mothers and older children an attempt is made to answer Halliday's queries concerning psychosomatic disease in general: "What sort of child is this? Why did he get the disease he did? Why did he get the disease when he did?"

The idea of this Play Clinic is not original, but was taken directly from Rogerson of Guy's, whose recent death we all so much deplore. He found in his clinic that nearly all the children showed an initial anxiety and lack of self-confidence, far greater than that usually seen. Some would scarcely play at all, and others only very cautiously with a few toys in a corner of the room. Soldiers and cannon were treated carefully and often with alarm. When the children became more confident their behaviour showed an aggressiveness and over-activity in marked contrast to their earlier play. During this phase of vigorous activity there was in most cases a striking clinical improvement, but relapses occurred if the children's freedom of self-expression was curtailed or thwarted in any way. He regarded this behaviour as typical of asthma and as expressing underlying emotional tension. Such things as over-anxiousness about school work and over-fussiness of mothers are obvious examples of situations productive of tension in a child (Rogerson, C. H. (1937): *Quart. J. Med.*, 24, 367).

We have failed to corroborate Rogerson's findings as regards the behaviour of our thirty children *at play*. They seemed on the whole to be normal. The older ones thoroughly enjoyed playing ping-pong and billiards. The quiet or shy little ones played happily with mosaics and jig-saws; the more boisterous ran about after balls and chased each other. Often, like all children, they ceased to play properly and simply "mucked about", threatening one another amicably with billiard cues and hitting the ping-pong balls wildly all over the room. It would have been quite impossible for an independent observer to pick out our asthmatics from among their normal brothers and sisters. Naturally the children vary—some are shyer than others—but do they differ as a group from normal children? We thought not, superficially, but to determine the point we asked the headmistress of a small school for a report on her fourteen healthy children. She said "one is antisocial and uncooperative; one completely home-ridden and with no desire to try anything at all difficult—mother overwhelmingly fussy and anxious; one very little go and no push, and one weeps too easily". She found them all excitable, and 100 per cent. were self-conscious, some more than others. All except the one, were cooperative in general games, obviously enjoying companionship and keen to do well at work. Our

children appear to come out of the comparison with hers quite creditably; we have no child that is antisocial and uncooperative, and only three abnormally shy retiring ones out of thirty.

The conclusion therefore is that we have not been able to learn anything positive about asthma from watching our children *at play*.

There are several possible reasons why the findings differ from Rogerson's. He was a psychiatrist and as such there would be a marked tendency for psychiatric cases to be referred to him. In support of this, ten of his patients were only children, whereas in our series the figure was only five out of a similar number. Again, being a psychiatrist it is quite certain that he would be both able and likely to read more into children's play than we would. Moreover, his controls were not normals but non-asthmatic problem children.

FACTORS PRECIPITATING ATTACKS

I now want to say something about what we learnt by getting to know the mothers and discussing with them the setting in which their children's attacks occurred. Several features immediately strike one. First, the rôle of excitement. In no fewer than fourteen out of thirty cases was excitement given by the mother as the main "cause" of the asthma. Here are some typical examples from the mothers' letters and statements:—

"Diana's attacks appear occasionally without any known cause but we have noticed that when she is looking forward to anything, such as examinations or going away for outings with the girl guides, she gets worked up and excited and the asthma appears before the event comes off".

"He gets all worked up before he gets an attack and bites his elder brother, a thing he never does at other times".

"James often gets asthma when he is excited about going away for a holiday or going to a party. I can't tell him he's going anywhere because he gets all worked up, has asthma and can't go".

Secondly, one cannot help being struck by the part played by infection: "It came on after whooping-cough"; "Every time he gets a cold off starts the asthma"; "He's been wonderful since he had his tonsils out"—all these remarks are common, and in fact we found them mentioned as major factors in fourteen of our cases. If in our series we take the emotional and infective triggers together we find that they are regarded as the "causes" by the mothers in twenty-four out of our thirty cases. Sometimes it is one and sometimes it is the other in the same patient—the mothers anyhow recognize what is meant by psychosomatic disease!

Thirdly, one is struck by the very few occasions in which the history suggested hypersensitivity to the common allergens (three of our cases only).

Fourthly, there is an equally small group in which the asthma appears to be precipitated by climatic conditions—fog, change of temperature, East winds and the like.

What do these observations mean? It is difficult to be sure. It seems reasonable to deduce that in asthma the bronchioles are a *locus minoris resistentiæ*, to be sent into spasm by stimuli which vary even in the same individual. When, however, excitement is the trigger it must be something different from the normal exuberance shown at the play clinic, otherwise we should be constantly witnessing attacks, whereas they are in fact very rare. The excitement which starts off the asthma appears to contain in it an element of tension, but we have been impressed by the fact that the tension is acute and not chronic. The homes, mothers and general background of these children appear reasonably normal but the child over-reacts, either to an ordinary tensional experience or to a quite trivial infection. He is in fact allergic in the widest possible sense.

Great stress has been laid by others on *chronic* tensional situations in the home but we have not been able to substantiate this. We must remember that life is not a bed of roses and that it is possible to discover sources of irritation and friction in all human lives and relationships. Perfection is not natural and only questionably desirable. The point I want to make therefore is that it is the child and not the environment that is mainly wrong. Trivial *normal* things start off asthma.

RESULTS

The results, as might be expected, are excellent. Unless there is gross deformity of the chest or much emphysema I am sure the majority of children do quite literally grow out of their disability as they become more stable in mind and body. Getting better, however, may be a tedious business with many fluctuations. Multiple causes call for multiple treatments and we find that in practice we treat most of our children at all levels—reassurance and explanation, sedation, avoidance of allergens, desensitization, breathing exercises and convalescent homes; most unscientific, but we rationalize it by saying that as many elements go to the re-creation of a healthy child as go to the winning of a long war, and I fully believe that it is only by a combined operation that victory can be achieved.

But the fight is often long, and the use of the play clinic is to provide a focal point where patients can be sure of receiving sympathy, time, encouragement and advice. We feel it is useful because they keep on coming, they write to us, responded in a body to the follow-up, and constantly express their gratitude for the interest which continues to be taken in them.

A NOTE ON ASTHMA

By A. V. MAGEE, M.B., CH.B.

Temporary Assistant Medical Officer of Health, City of Manchester.

THE following cases of asthma are described in the hope that they will stimulate an interest in the possibility of a sex factor existing in all cases of spasmodic asthma. It is well known that the disease appears in the mansion, the manor and the manse—rarely in the dirty dungeons of the down-and-outs. Although the cat, the dog and the pollen-laden bee are blamed for it, they never suffer themselves. My lady's soft feather pillow plays its part, but the harlot's blankets are not suspect. The intellectual suffers: the sex-satisfied escape.

(1) I brought Aubrey in my "little black bag" to wealthy middle-aged parents, and he flourished exceedingly until six years of age. Then, one evening, he surprised his parents and, no doubt, himself, by developing a perfect attack of asthma. In spite of the advice of relatives and friends, who suggested filling him with tablets of Ko-Ko, Mo-Mo, To-To and other sovereign remedies, he continued to have his attacks soon after climbing into his luxurious cot. He never had an attack, however, when he slept in the same room as his parents.

One morning I was called in to see his mother, and on being shown into the drawing-room found little Aubrey warming his back at the fire with his hands in his pockets. He was panting away like an old man and vigorously touching his "little man". That evening I rang up his father and suggested a cure for the asthma. He rang off in a violent temper. Still, with a bit of persuasion, a cure was obtained and the asthma accompanied the foreskin into oblivion.

(2) The first time I met Ethel she was thirty-four and had suffered from asthma since the age of twenty-one. The attacks came on forty-eight hours before the period and lasted until the flow was at its height. Ethel, in an attack, was like Old King Cole—she "called for her fiddlers three". Her loving parents took turn about spraying her throat with adrenaline until such time as I could arrive with the needle. Occasionally I tried morphine or sterile water, but they never worked.

Ethel was in love with, and was beloved by, an elderly married man in her own profession and as he could rarely escape from his married ties, adrenaline had to play the part of the lover. This dawned on me one evening when I entered the bedroom, unannounced, and found the patient panting away quite happily whilst the boy friend massaged the left breast. A few weeks after this incident, the lover met an accidental death and the patient developed a very severe attack of asthma. A specialist, called in, advised removal to hospital in the morning. At 9.30 a.m. she had arrayed herself like Lady Jane Grey for the scaffold. The ambulance men trudged upstairs with the stretcher, and entered the bedroom to find her dead.

(3) Stephen had a good job and an ugly wife. He also had asthma. His firm, loth to have such a good man off sick so often, paid for him to have a month's treatment in Switzerland where a director had received much benefit. Letters and photographs soon proved the medical wisdom of the firm's decision. One snap showed Stephen leaping four feet into the air hand in hand with a pretty Swiss nurse.

The month was up and we all looked forward to the miracle's return. On the train from Harwich, however, he had a slight attack of asthma—due, no doubt, to the smoke and grime. Arriving home he took to bed and ordered his wife to get out the syringe and adrenaline. I don't know the exact cause of death for a friend took over the case as I went on holiday just then.

) It may seem strange but I always thought Mabel got a certain amount of satisfaction from the great alarm and distress her parents suffered when she attacks of asthma. I wasn't the first to attend the patient. Like the lady mentioned at Mark, she had suffered many things by many physicians and her parents had it all they had and were nothing bettered but rather she grew worse. Eventually left her "mouldy old people" and asthma left her when a married man with a hidden wife set her up in a flat.

) Beatrice was the local schoolteacher and as fit as a fiddle. When she married the lay-preacher and Man of God, we all thought it was an ideal match. After a few months of marriage, however, Beatrice developed attacks of asthma coming about 11.30 p.m. On investigation it appeared she finished her household duties at 10.30 p.m. and went to bed, leaving her husband poring over Matthew's commentary on the Bible". He retired about 11 p.m., switched off the bedroom light, disrobed in the dark and with his mind full of spiritual things, crept into bed and fell fast asleep.

On a talk with his wife I learned that from her earliest days she had a tremendous desire to have children of her own. When she informed her husband of this he rebuked her, saying that those who revel in, or even think of, the pleasures of procreation, sin in the eyes of the Lord. The husband was seen and the duties of a married man explained to him. Beatrice now has three children and asthma is forgotten.

THEORY

We know that asthmatics love adrenaline. We know that changes in the suprarenals cause altered sex characteristics. We know that the hormone-producing organs are linked together like a ship's cable. If one link breaks, the ship is "at sea".

I suggest that asthmatics snap their cable at the suprarenal link and repair it with the mental satisfaction given by adrenaline injected (through their parasympathetic system) or by an increased adrenaline output stimulated by sexual satisfaction.

TREATMENT

General practitioners dealing with cases of true spasmodic asthma should have a "knee to knee" talk with their patients and unravel any sexual difficulties existing. This sounds simple enough, but asthmatics can be very uncooperative and frequently antagonistic. It may mean losing the patronage of a good percentage of them but that will save quite a few urgent night calls. If this approach fails there are always our old friends bromide and morphine, in large doses, available for use before an attack is likely to come, and its timing can be gauged by the talk mentioned above.

CARE OF THE PERINEUM DURING LABOUR

By WILLIAM HUNTER, M.D., M.R.C.O.G.

Assistant Obstetrician, Princess Mary Maternity Hospital; Associate Surgeon to the Gynæcological Department, Royal Victoria Infirmary, Newcastle upon Tyne.

THE comfort of the patient following childbirth depends to no small degree upon the presence of an efficient pelvic floor and an intact perineum. The occurrence of maternal damage during labour has been recognized from time immemorial, and we have even been told in the *Book of Genesis* that Perez, the son of Tamar, born about 1727 B.C., was so named because he inflicted a tear upon his mother at the time of his birth. Yet, in his lectures delivered nearly two hundred years ago, William Hunter gave more practical advice regarding the prevention of maternal birth injury than many of the modern textbooks. In spite of this lack of attention during recent years, however, much can be done to reduce the risk of perineal trauma by proper management of labour, and to prevent lasting discomfort and incapacity by careful repair of lacerations.

The chief causes of perineal laceration are relative disproportion between the fœtus and the vaginal orifice, too rapid expulsion of the fœtus, the passage of unnecessarily large sectional planes of the fœtus through the vaginal orifice due to faulty mechanism and, occasionally, posterior displacement of the fœtal head at the pelvic outlet by an acute sub-pubic angle.

ASSISTANCE AT DELIVERY

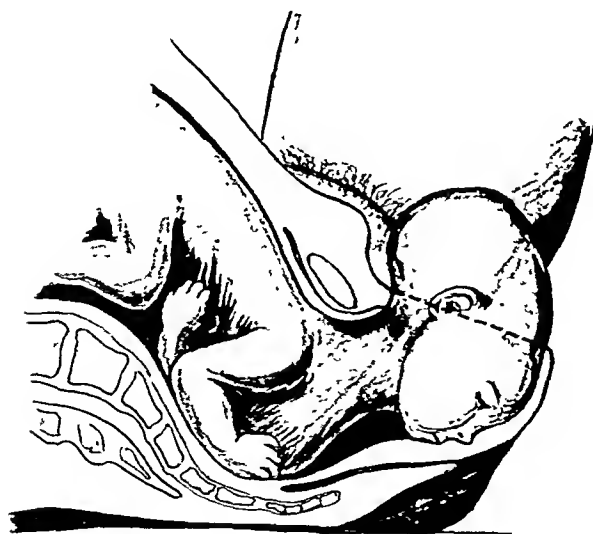
Assistance at delivery is intended to help the mechanism most favourable for the normal birth of the baby and thereby to reduce the risk of injury to the mother and to the child. Deliberate unhurried delivery of the head, with gradual stretching of the perineum, is the first essential.

As it expands the vaginal orifice, the head is kept well flexed by drawing the occiput away from the pubes with the fingers of the right hand, the thumb resting lightly on the sagittal suture as near as possible to the anterior fontanelle to guard against a sudden, unexpected and uncontrolled descent and forward thrust of the head. Maintenance of flexion by pressure through the perineum is not recommended as it carries a risk of damage to the pelvic floor. Adequate time is allowed for completion of internal rotation of the head. The occiput is freed by slipping back the anterior margin of the vaginal orifice, the vestibule and the labia minora to the nape of the neck at frequent intervals during uterine contractions while the vertex is descending, to ensure that the smallest possible sectional planes of the head pass through the vaginal outlet (fig. 1 and 2).

When the occiput is born, the forward thrust of the head may be assisted and extension initiated by pressure on the brow through the ano-coccygeal segment of the perineum with the fingers of the left hand (fig. 3), extension being continued by traction on the bi-temporal diameter by the fingers of the right hand, the patient



IG. 1.—Birth of the foetal head showing the disengaging diameter before the occiput has been freed from the vestibule.



IG. 2.—Birth of the foetal head showing the disengaging diameter after the occiput has been freed from the vestibule.

CARE OF THE PERINEUM DURING LABOUR

By WILLIAM HUNTER, M.D., M.R.C.O.G.

Assistant Obstetrician, Princess Mary Maternity Hospital; Associate Surgeon to the Gynaecological Department, Royal Victoria Infirmary, Newcastle upon Tyne.

THE comfort of the patient following childbirth depends to no small degree upon the presence of an efficient pelvic floor and an intact perineum. The occurrence of maternal damage during labour has been recognized from time immemorial, and we have even been told in the *Book of Genesis* that Perez, the son of Tamar, born about 1727 B.C., was so named because he inflicted a tear upon his mother at the time of his birth. Yet, in his lectures delivered nearly two hundred years ago, William Hunter gave more practical advice regarding the prevention of maternal birth injury than many of the modern textbooks. In spite of this lack of attention during recent years, however, much can be done to reduce the risk of perineal trauma by proper management of labour, and to prevent lasting discomfort and incapacity by careful repair of lacerations.

The chief causes of perineal laceration are relative disproportion between the fœtus and the vaginal orifice, too rapid expulsion of the fœtus, the passage of unnecessarily large sectional planes of the fœtus through the vaginal orifice due to faulty mechanism and, occasionally, posterior displacement of the fœtal head at the pelvic outlet by an acute sub-pubic angle.

ASSISTANCE AT DELIVERY

Assistance at delivery is intended to help the mechanism most favourable for the normal birth of the baby and thereby to reduce the risk of injury to the mother and to the child. Deliberate unhurried delivery of the head, with gradual stretching of the perineum, is the first essential.

As it expands the vaginal orifice, the head is kept well flexed by drawing the occiput away from the pubes with the fingers of the right hand, the thumb resting lightly on the sagittal suture as near as possible to the anterior fontanelle to guard against a sudden, unexpected and uncontrolled descent and forward thrust of the head. Maintenance of flexion by pressure through the perineum is not recommended as it carries a risk of damage to the pelvic floor. Adequate time is allowed for completion of internal rotation of the head. The occiput is freed by slipping back the anterior margin of the vaginal orifice, the vestibule and the labia minora to the nape of the neck at frequent intervals during uterine contractions while the vertex is descending, to ensure that the smallest possible sectional planes of the head pass through the vaginal outlet (fig. 1 and 2).

When the occiput is born, the forward thrust of the head may be assisted and extension initiated by pressure on the brow through the ano-coccygeal segment of the perineum with the fingers of the left hand (fig. 3), extension being continued by traction on the bi-temporal diameter by the fingers of the right hand, the patient



FIG. 1.—Birth of the foetal head showing the disengaging diameter before the occiput has been freed from the vestibule.

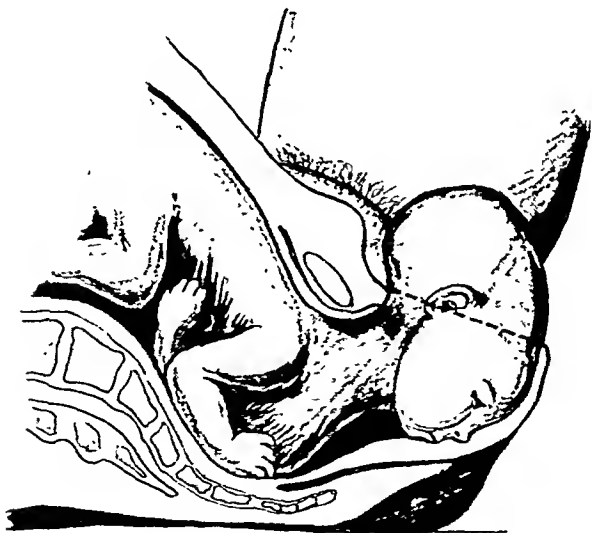


FIG. 2.—Birth of the foetal head showing the disengaging diameter after the occiput has been freed from the vestibule.

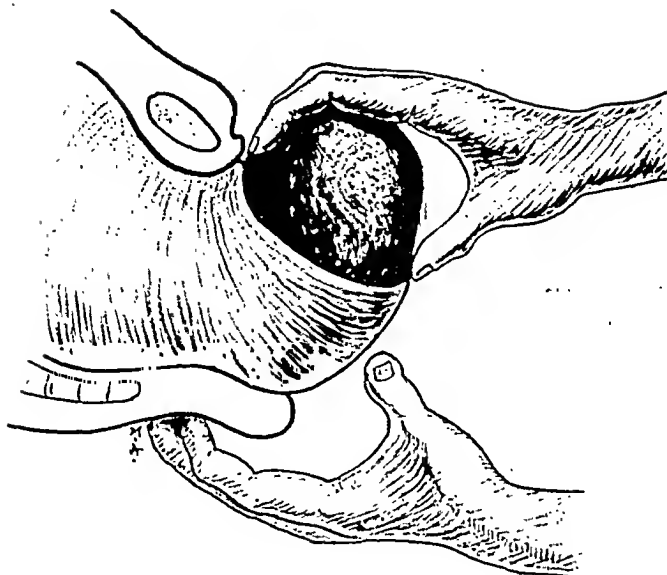


FIG. 3.—Completion of the forward thrust of the fetal head during primary extension aided by ano-coceygeal pressure.



FIG. 4.—A case of stress incontinence of urine showing a healed anterior vaginal laceration and an intact perineum.

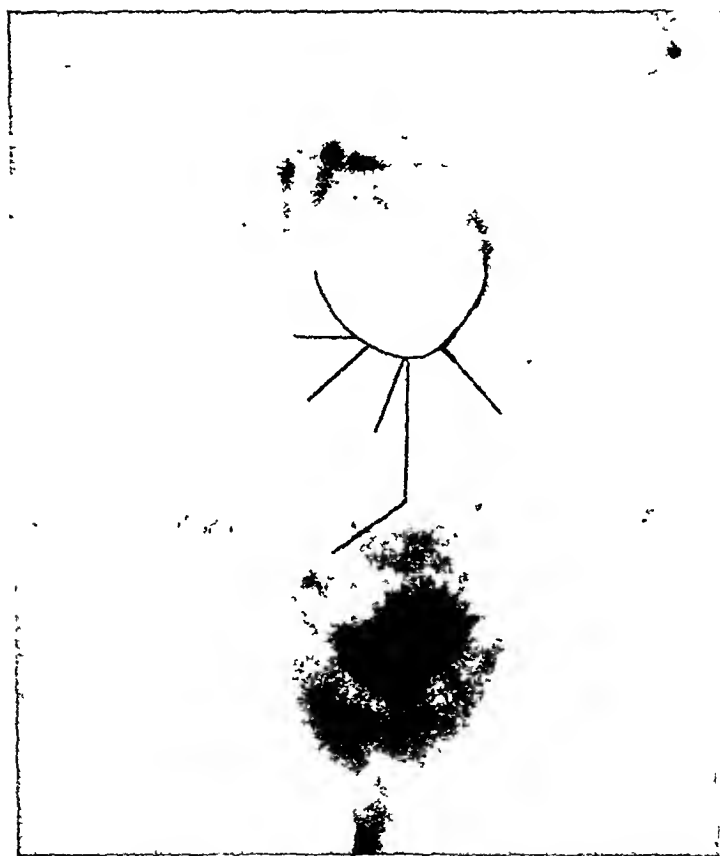


FIG 5—Lines of incisions for episiotomy. The lateral and postero-lateral incisions are not recommended

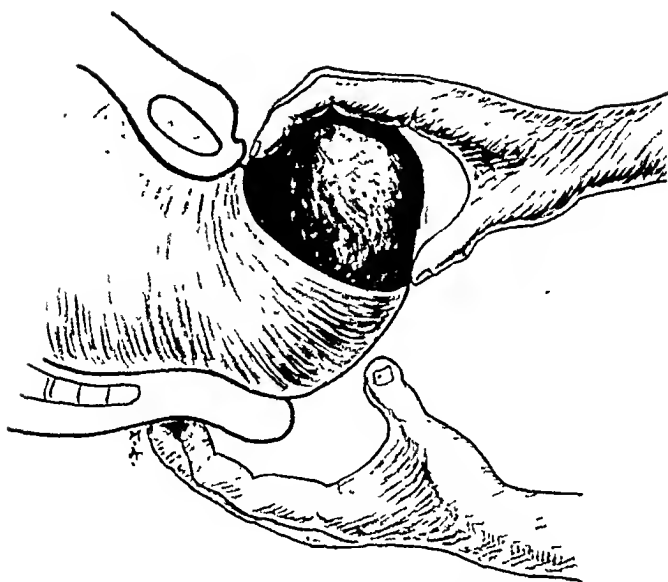


FIG. 3.—Completion of the forward thrust of the fetal head during primary extension aided by ano-coccygeal pressure.



FIG. 4.—A case of stress incontinence of urine showing a healed anterior vaginal laceration and an intact perineum

breathing deeply or, preferably, being under light surgical anaesthesia. Lateral support may be given by the left hand to the slackening perineum after the birth of the brow as the irregular face is being disengaged, and the chin is freed by sweeping the finger from one angle of the jaw beneath the chin to the opposite side. The administration of the anaesthetic is now discontinued. The toilet of the eyes, nose and mouth is carried out and the presence of "cord round neck" is eliminated, while ample time is allowed for restitution and external rotation of the head, with internal rotation of the shoulders, to take place. The anterior and posterior shoulders, the trunk and limbs are carefully delivered in turn, torsion and excessive lateral flexion of the neck being avoided.

If the size of the vaginal outlet is inadequate or laceration of the perineum is impending, the head resting on the pelvic floor may fail to advance farther in spite of powerful uterine contractions and good cooperation on the part of the patient, depression of the perineum not being accompanied by further dilatation of the vaginal orifice. In some cases the perineal skin may blanch during the contractions and may show beading with serum. Multiple small irregular skin fissures showing a tendency to bleed occasionally appear, and a minor trickle of blood may come from a superficial laceration of the lower third of the posterior vaginal wall. In other cases an indistensible ring of almost cartilaginous consistency may be felt within the vaginal orifice immediately above the hymen. Often a secondary caput succedaneum develops on the scalp and enlarges progressively.

LACERATION OR EPISIOTOMY

When the vaginal orifice is unable to expand sufficiently to permit the passage of the foetus, if labour is allowed to proceed unchecked, sooner or later the perineum will give way, and an irregular lacinate rent will result, its direction and extent being uncontrolled except by the correct and skilful control of the foetal head during delivery. Further, considerable force is required to rupture the resistant perineum and the full stress is taken by the foetal head. There is therefore an appreciable risk of intracranial trauma which, even though it may often be of minor degree, cannot be other than harmful to the child. This is particularly liable to occur in small babies. It is possible to be over-zealous in the care of the perineum at the expense of the anterior vaginal wall. A perineal laceration may be repaired efficiently with relative ease but an anterior vaginal laceration may be associated with damage to the voluntary sphincteric mechanism of the urethra, causing stress incontinence of urine, a condition which is notoriously difficult to treat (fig. 4). On the other hand, when laceration is inevitable or the advance of the foetal head is arrested by rigidity or inelasticity of the vaginal orifice, deliberate division of the perineum with scissors, if performed intelligently and with prudence, will prevent unnecessary suffering by shortening the second stage of labour, will minimize the risk of overstretching or damaging the anterior vaginal wall and the underlying structures and, by deflecting the wound, of damaging the anal sphincters and canal. It will also lower the



FIG. 6.—Diagrammatic representation of the tissues to be sutured after episiotomy. The author uses a single strand of catgut.

lower birth canal, minimize disorders of micturition and defæcation, and reduce the risk of traumatic intracranial lesions in the child, especially when it is premature. After episiotomy, the foetal head should be delivered with care, to prevent extension of the wound, special attention being directed to the completion of internal rotation, the maintenance of adequate flexion until the occiput is born, the displacement of the vestibule to the nape of the neck before extension is permitted to take place, and slow delivery of the head.

PERINEAL REPAIR

A good episiotomy, carefully repaired, as it reduces the forceps rate and, when judged by the findings at postnatal examination, is found to give good anatomical and functional results, is a conservative procedure. Every patient should be carefully swabbed and examined for perineal or vaginal laceration as soon as the cord has been severed after delivery and, if an episiotomy has been performed, its precise extent should then be determined.

In an inquiry conducted by the Medical Women's Federation (1949) it was found that in a series of 425 confinements, over two-thirds of which were attended by specialist obstetricians, perineal repair was necessary in 69 per cent. of primigravida, 44 per cent. of secundigravida, and a diminishing percentage of multigravida.

No matter how trivial the laceration may appear it should be efficiently repaired. In the case of the smaller lacerations or episiotomy incisions, the repair may be carried out on the bed with the patient in the dorsal position with the knees drawn up and widely separated, but in the more extensive cases, the modified lithotomy position, maintained by an obstetric helper, Clover's crutch, chairs at the bedside, or assistants, is essential. It is presumed that the vulva has been efficiently shaved before delivery, as asepsis is impossible when hair, which tends to be caught up in sutures or to be incorporated in the wound, or later, becomes matted with lochial blood, has not been removed. A general anaesthetic may be used for perineal repair, but about 5 to 10 ml. of 2 per cent. local anaesthetic injected subcutaneously through the wound edges on either side gives very satisfactory results. Five per cent. dettol solution—a full ounce to the pint—is a satisfactory antiseptic to use for swabbing the vulva, and sterile gloves should be worn. Sterile towels are a boon as a covering for the instrument table (or chair) and for covering the bed and other parts likely to be touched by the ends of the suture material. If dry sterile towels are not available, towels or clean babies' napkins can be used after boiling for ten minutes or steeping in 1 in 20 dettol lotion for twenty to thirty minutes. These can readily be prepared as routine before the delivery with towels (or napkins) required during the course of the delivery itself. I use a number 2 half-circle medium triangular skin needle for all suturing, with number 0 B.P.C. Merson's 21-day catgut,

forceps rate, facilitate subsequent good apposition of the tissues and perineal repair by leaving a clean-cut surgical incision in a pre-selected position instead of an irregular lacinate contused wound, and will reduce the hazard of intracranial trauma. If the wound is efficiently sutured a good anatomical and functional result is nearly always obtained and accurate approximation of the tissue during perineal repair is facilitated.

TECHNIQUE OF EPISIOTOMY

The operation of episiotomy should be delayed whenever practicable until the perineum is under tension, when the deeper structures will be displaced from the line of the incision. The patient may be lightly anæsthetized or a local anæsthetic may be injected into the perineum. If the head cannot be fixed in its position of maximum descent by pressure on the uterine fundus when a contraction has passed its peak, the perineum should be stretched laterally and firmly depressed by the separated index and second fingers of the left hand introduced into the vagina while the incision is being made. This digital stretching must, however, be considered inferior to expansion by the advancing fœtal head. The incision should not, as a rule, be made at the height of a contraction and the left hand should be held in readiness to control the swift descent of the released fœtal head.

Choice of incision.—The choice of incision is of considerable importance (fig. 5).

A lateral incision gives little increase in the space available for the fœtal head to pass through, there is some possibility of inflicting damage upon branches of the internal pudental artery, and unequal retraction of the wound edges with deep recoil of the divided levator fibres renders accurate apposition and repair difficult. A median posterior incision gives a maximum increase in available space with little irreparable damage to the underlying structures, straightforward repair with a minimum amount of tension on sutures, and satisfactory healing in nearly all cases, its only disadvantage being the risk of laceration of the anal sphincters and canal if extension occurs. The risk may be obviated by converting it into an L-shaped incision, the lower limb of which passes through the tissues antero-lateral to the anal sphincter without dividing any essential structures. If it is thought that only a relatively small episiotomy incision will suffice, a modification of this incision is sometimes used. The perineum is divided posteriorly from the mid-point of its anterior margin and the incision is deflected slightly to the right side so that any prolongation will reach the sphincters at a tangent. It is stressed that such an incision must start in the midline in front and must be deflected only slightly to the side. The postero-lateral incision starting to one side of the midline and extending postero-laterally at an angle of approximately 45 degrees is intermediate in advantage and disadvantage between the posterior and lateral incisions, and is not recommended. Bilateral postero-lateral incisions should be condemned as the increase in available space at the vaginal outlet is no greater than that obtained by a single posterior incision, whilst the centre flap retracts, is difficult to suture in position and, after repair, usually forms an atrophic, inefficient perineum consisting of little more than vaginal mucosa and perineal skin. Undoubtedly the incision of choice is the median L-shaped incision or the median tangential incision.

A timely episiotomy, if properly performed and efficiently sutured, will restore the integrity of the maternal tissues, prevent overstretching of the

THERMAL COMFORT IN TEMPERATE CLIMATES

By W. S. S. LADELL, M.B., B.Ch.

From the Colonial Medical Research Committee's Laboratory for Research in Hot Climate Physiology, at the Medical School, Yaba, Lagos, Nigeria.

EXCEPT in the most unusual circumstances a man always loses heat to his environment, and in all circumstances he is generating heat. When the rate of heat loss tends to exceed that of heat production the individual feels chilly: when the reverse occurs, either because of increased heat production or because of difficulties in the way of heat loss, he feels warm. At all times, however, the body temperature is kept between narrow limits, first by immediate adjustments, which have the effect of altering the heat stored in the body, and then by re-establishment of the equilibrium between heat loss and heat production, by alterations in the one or the other. To be in thermal equilibrium is not necessarily to be in thermal comfort; but thermal comfort is a special case of thermal equilibrium in which no changes in heat storage are taking place and in which adjustments, either to the heat loss mechanism or to the heat production, are minimal.

The chief means by which the temperature is regulated is adjustment of the heat loss mechanisms. Heat is lost directly by conduction, convection and radiation. The amount of heat transferred by conduction depends upon the area of contact between the hot object and the conducting mass; for a sitting or standing man the area of contact with a solid mass is small, and as the thermal conductivity of the air is low, the heat loss by conduction is negligible. But if a man is immersed in water, heat loss by conduction (and also by convection) is more rapid. A naked man can survive for at least four hours in air at 34° F. (1.1° C.), but immersion in water at that temperature may cause fatal chilling in less than half an hour (Molnar, 1946).

Convection and radiation are the two main routes of heat loss in temperate climates. Heat loss by convection depends upon the temperature difference between the cooling surface and the air flowing over it; it is also affected by air movement. Radiation loss is a function of the temperature difference between the surfaces concerned and is also dependent upon the nature of those surfaces. Some surfaces absorb all incident radiation and also radiate perfectly; such surfaces are described physically as "black". Human skin of any colour, the surfaces of clothes and most painted surfaces are of this type, insofar as low temperature radiation is concerned. In addition some cooling by evaporation is always taking place; inspired air takes up moisture as it passes along the respiratory passages, 300 to 400 ml. per day is evaporated this way; and there is a continuous flow of water through the non-sweating skin by osmosis, the insensible perspiration. The amount of heat lost by evaporation, the insensible water loss, is equal to 25 per cent. of the basal metabolic heat.

Heat losses cannot be reduced beyond a certain point. Evaporative loss always continues, and loss by the other routes can only be reduced, but never

or number 00 B.P.C. London Hospital 21-day catgut for the vaginal and muscular layers and number 4 T black braided or waxed silk for the perineal skin. This is reliable, easy to handle and does not prick the patient during the puerperium as does silkworm gut or nylon. Only dyed sutures should be used for the perineal skin, as undyed non-absorbable sutures may be difficult to find when the perineal hair begins to grow.

I start by identifying and transfixing the apex of the laceration in the vaginal wall with the needle (fig. 6) and close the vagina by a continuous mattress suture—the stitches being inserted close together to avoid puckering and shortening of the vaginal wall and every stitch being “looped”. This makes a firm, hæmostatic closure through which lochia cannot pass into the deeper layers of the wound. The left levator ani muscle is picked up, the needle being passed from the superficial to the deep aspect and being drawn completely through before the right muscle is picked up from the deep to the superficial aspect to avoid damage to the rectal wall. This stitch is used as a retractor to draw the muscle bellies into greater prominence, as at least one interrupted levator stitch is inserted in front and one behind it, and all sutures are then tied. A slightly paler layer of superficial perineal muscles and supporting tissues overlying the levator muscles is then brought together by interrupted catgut sutures to add bulk to the perineum, to bring together the retracting superficial fibres of the levatores ani, and to bring the skin edges into apposition. Finally the skin—and the skin alone—is closed by interrupted black silk sutures tied without tension and with the ends left about an inch long for ease of identification.

The repaired perineum is swabbed down and sprinkled with sterile sulphanilamide powder before a sterile vulvar pad is applied. The patient is nursed in Fowler's position, preferably on an air-ring. If a nurse is in residence the vulva should be swabbed with 1 in 40 dettol lotion, followed by dusting with sulphanilamide powder, whenever the patient passes urine or has her bowels opened. If there is no nurse in residence I think it is wise to say that the anus only is to be swabbed with a wool pad steeped in dettol lotion after defæcation and the vulva is not to be touched except by the visiting nurse. Clean sterile pads should be put on whenever the pad is soiled, and an aperient is given on the second night after delivery. The silk sutures are usually removed on the sixth day and the results are remarkably good, so good, in fact, that it is sometimes difficult to find a perineal scar at the time of the postnatal examination six or eight weeks after delivery.

I should like to express my thanks to the publishers, Messrs. John Sherratt and Son, and Messrs. D. Appleton, Century Co., Inc., for permission to reproduce illustrations from the *Journal of Obstetrics and Gynaecology of the British Empire*, and from J. W. Williams' “Textbook of Obstetrics” (third revision by H. J. Stander), respectively.

References

- Hunter, W. (1943): *J. Obstet. Gynaecol. Brit. Emp.*, 50, 260.
 Medical Women's Federation Report (1949): *Brit. med. J.*, 1, 333.

dilated vessels. A flushed or pink skin is always warm, but a pale skin may be hotter than a red skin if the circulation in the deeper parts is rapid; this may be brought about in man, especially in the finger tips, by the opening up of the arteriovenous anastomoses; these open both when there is local cooling, and so serve to keep up local skin temperature, and when the environmental temperature is high and heat loss by the direct routes is failing. Bazett (1938) has shown that the local skin circulation may be increased ten times in response to heat; this puts a considerable strain on the cardiovascular system, and to maintain the arterial blood pressure the cardiac output rises and there is vasoconstriction elsewhere; nevertheless, there is often a small drop in the arterial blood pressure of men during hot weather, and an unacclimatized man suddenly exposed to severe heat may suffer such a fall as to have syncope: he could be truly described as suffering from "heat shock". Early in acclimatization, however, there is an increase in the plasma volume which eases the vascular situation.

NERVOUS CONTROL

Heat loss, heat conservation and heat production are controlled by the hypothalamus. The centre controlling sweating is anterior in the supra-optic region; the other centres are lateral and posterior. Damage to the hypothalamus therefore upsets heat regulation; usually the anterior centres are more affected, as, for example, in cerebral malaria, and there is hyperthermia. The efferent impulses from the centres are mediated chiefly through the sympathetic, but the central stimulus for shivering is believed to pass down the spinal cord. The centres themselves are controlled reflexly from end-organs in the skin, and they are also sensitive to changes in the blood temperature locally. The stimulating effect upon the metabolism of adrenaline and, when exposure periods are long, of thyroxine, are important when an individual is exposed to cold, and are part of the general endocrine control of metabolism.

THERMAL COMFORT

Over a narrow range of air temperature no adjustments are necessary for thermal equilibrium and there is thermal comfort. For nude resting males this range is from 82.4 to 88.8° F. (28.0 to 31.6° C.) and for women from 80.6 to 90.6° F. (27.0 to 32.6° C.). Within this comfort zone, heat production is at its lowest and the skin is moderately vasodilated and not sweating. Any rise in air temperature above these limits, or any increase in metabolism or activity, results in sweating and a rise in body temperature; thermal equilibrium is maintained, however, although at successively higher body temperatures as the environmental temperature rises or the metabolism increases, until the body temperature reaches about 105° F. (40.6° C.). At this point the regulating mechanism fails, and unless active cooling is initiated the body temperature continues to rise, until irreparable damage is done to the brain and the patient dies. Fever is not in itself harmful until

stopped, by cutting down the circulation to the skin and subcutaneous tissues. Erection of the skin hairs will reduce losses from the naked body by preventing the free flow of air over the skin; but the best insulation the unaided body can achieve is only equal to that of a layer of cork of the same thickness as the skin and subcutaneous tissues.

BODY TEMPERATURE AND THE VASCULAR SYSTEM

Heat results from the metabolic processes. This heat is picked up by the blood and distributed to all parts of the body, in the same way as the heat from the furnace is distributed throughout a building by the water in the pipes of a central heating system.

The skin and superficial tissues are always cooler than the blood and deeper tissues, as they are continually losing heat to the environment (in temperate climates); they are much cooler when the circulation is closed down. The depth below the skin surface at which the tissues are at the (central) blood temperature varies according to the state of the skin circulation, and the total heat content of the body is a function, not only of the central temperature, but also of the thickness of this cooler layer. The more blood to the skin and subcutaneous tissues the thinner this layer is, and so the greater the total heat content; when the circulation is cut down the layer becomes thicker and cooler and the total heat content is less. Thus small changes in the heat stored in the body can occur without any gross changes in the central temperature, the result of alterations in the skin circulation. Sudden or marked alterations in the peripheral circulation may, however, result in temperature changes centrally; for example, most individuals suddenly exposed to a high environmental temperature show an initial drop in rectal temperature of $\frac{1}{2}^{\circ}$ F. as the skin circulation opens up reflexly and the superficial tissues are warmed up by the blood.

The rate at which heat passes out from the tissues within depends upon the blood flow through the skin and upon the temperature difference between the skin surface and the deep tissues. The steeper the thermal gradient, i.e., the cooler the surface, or the warmer it is internally, the greater will be the flow of heat, if the circulation is unaltered. The internal temperature depends primarily upon the rate of heat production, but the surface temperature is determined, not only by the rate at which heat reaches it, but also by the rate it is losing heat to the environment. The factors concerned in skin temperature are therefore complex; and, although when heat losses are impeded or production rises the skin is warmer than if there is a tendency for losses to exceed production, skin temperature is not a satisfactory index either of thermal equilibrium or of all the adjustments that are being made to maintain it.

The circulatory changes in the skin are shown by the colour. When the vessels, especially those more superficial, are constricted the skin is pale. A red skin indicates a rapid flow of blood through dilated superficial vessels, and a blue, cyanosed, skin shows slowing of the circulation in otherwise

radiant temperature and the air temperature are similar; but they differ in certain circumstances: e.g., in the presence of hot machinery when radiated "wild heat" may make conditions intolerable, and at sea, where the wide surface of cold water and the cold sides of the ship make those on board feel considerably cooler than they would be at the same air temperature on land. Radiation on the head is said to be uncomfortable, but there is no physiological basis for this; the importance of "nose closing" radiation (so called by Sir Leonard Hill) has been much overrated; there is considerable doubt whether in fact it does exist (Bedford, 1948).

Dufton (1936), in his equivalent temperature scale, takes radiation into account; equivalent temperature integrates dry bulb temperature, air movement and radiation; it is defined as: "that temperature of a uniform enclosure in which, in still air, a black body of sufficient size would lose heat at the same rate as in the environment, the surface temperature of the body being one-third of the way between the temperature of the enclosure and 100°F. (37.8°C.)". It may be measured by means of the eupatheoscope, or it may be derived from independent measurements of the three separate factors. At low air movements and in the absence of much radiation it is very nearly equal to the dry bulb temperature; but as it does not take wet bulb temperature into account its use should properly be limited to temperatures below 75°F. (23.8°C.).

CLOTHING AND THE EFFICIENCY ZONE

A naked inactive man in relatively still air of moderate humidity is in thermal comfort at air temperatures between 83° and 88°F. (28.3 to 31.1°C.); this temperature range is close to that found in tropical Africa (personal observations at Yaba, near Lagos, showed that there were over 600 days, between October 1946 and October 1948, when the shade temperature went above 83°F. , and over 350 days when it was over 88°F.); here the indigenous man is, for the most part, inactive and naked. Any activity at temperatures in the comfort zone leads to sweating; a non-resting man requires, for true comfort, a lower temperature; whilst clothes, by their insulating effect, diminish heat loss and make lower temperatures comfortable even at rest.

Markham (1947) considers that, for efficient hard work, the air temperature should be below 76°F. (24.4°C.) for lightly clothed men, and for a naked or near naked man 3° higher; he puts his lower limit at 60°F. (15.5°C.), giving a wide efficiency zone of from 60° to 76°F. (15.5 to 24.4°C.). Comfort zones worked out by other authors all fall within this range.

The outdoor climate in England and in temperate zones generally is well below the efficiency zone; the mean annual temperature in the United Kingdom is only 49°F. (9.4°C.). Man must therefore make his own climate, either a personal micro-climate under his clothes or in bed, or, by suitable heating and ventilation, a local indoor climate.

Clothes, by their thermal insulating power, diminish the potential losses by convection, conduction and radiation; but, except in environments where the temperature of the unclothed body would fall, the total amount of heat lost by these three routes together is not much less in the clothed than in the nude individual. Clothes may be considered as an extension of the skin: cooling takes place from the clothing surface and not from the skin; the

this point, 105°F. (40.6°C.) for most individuals, is passed; but once it is passed the patient is in danger of burning himself up, and he must be treated like any other fire and "put out". He should be cooled down as rapidly as possible, if necessary by spraying with water under a fan.

In environmental temperatures below the comfort zone heat loss is checked by progressive *reduction in the skin circulation*. The resultant cooling of the skin and subcutaneous tissues renders immediately available a small amount of stored heat, and keeps the thermal gradient, skin/environment, from increasing unduly. The increased thickness of the insulating tissue between warm interior and cold skin keeps the gradient, deep tissues/skin, also about the same. The net result is that radiation and convection losses are practically unaltered over a zone of about 10°F. , the zone of vasomotor, or physical, heat regulation. At these air temperatures, however, the body temperature falls slightly; when there is a drop of 1°F. , or after exposure for some time at 73°F. (22.7°C.), chemical heat regulation comes into play, the metabolism being increased centrally and also, by shivering, in the muscles. This increase in heat production is adequate at first, but at air temperatures below 50°F. (10°C.) heat loss outstrips production, body cooling is accelerated, and fatal chilling eventually occurs.

As evaporation of insensible perspiration goes on at all temperatures, *humidity* might be considered to have an effect on thermal comfort. The more humid the air the less rapidly will evaporation take place and so the warmer is the skin, but except at high temperatures and at extremes of humidity this effect is small. Bedford (1948) has calculated that in calm air at 70°F. (21.1°C.) a change in the relative humidity of 50 per cent. is equivalent to a change in air temperature of only 3°F. ; in general until the temperature reaches 75°F. (23.9°C.) humidity exerts no great effect on sensations of warmth.

Air movement is another environmental factor; in still air, heat loss by convection is much less than when the air is moving. The subjective feeling of warmth is much greater in stagnant air than would be expected from the air temperature and humidity.

The physiological effect of low air movement was shown at high air temperatures by Dunham and his co-workers (1946): for men working in overalls, decreasing the air movement from 100 ft. min. to *nil* was approximately equivalent to increasing the dry bulb temperature from 90 to 100°F. (32.2° to 37.8°C.). Bedford (1948) has shown, however, that although the invigorating effect of air movement is more noticeable at high temperatures, the effect of air movement on sensations of warmth is more marked at low temperatures. Houghton and Yaglogou (1923, 1924), in their "effective temperature scale", take both air movement and humidity into account. The effective temperature of an environment is that temperature of still air, saturated with water vapour, in which the equivalent sensation of warmth would be experienced. There is one scale for men in ordinary clothing, and another for men stripped to the waist. The scales were originally based on subjective sensations, but it has since been shown that the physiological effects of environments at the same effective temperature are the same, except at low air movements and at high temperatures and humidities.

The fourth environmental factor is *radiation*. Commonly the mean

perspiration, 590 calories of heat are saved by the system (body+clothes), but soggy clothes are not good insulators so more heat may be lost by conduction and convection later.

OUTDOOR CLOTHING AND PROTECTION AGAINST COLD

The same considerations apply for outdoor clothing as for indoors, but there are two points to be remembered. First, the more clothes worn the bulkier is the clothed body; this not only makes activity more difficult, but also increases the surface area, even ordinary clothes increase it by 16 per cent.; this tends to increase heat losses by conduction, convection and radiation. For any given environment there is an optimum thickness of clothing beyond which the disadvantage of increasing the surface area outweighs the gain in insulation. This particularly applies to gloves, sleeves and leg coverings, where the part protected is relatively thin; fingerless gloves can be made thicker than gloves with fingers, and sleeping bags thicker than trouser legs. The same problem is familiar to engineers lagging boilers and steam pipes.

The second point is activity: a thickness of clothing sufficient to keep an inactive man warm will be excessive as soon as he starts to work; metabolic heat will be retained within his clothes and soon conditions will be reached when he begins to sweat. If the water vapour from the evaporation of the sweat can diffuse through to the outside, this is only uncomfortable, but if there is such a thickness of clothing that condensation takes place in the more superficial layers, body cooling fails and there is danger of heat exhaustion. This problem has been examined in detail for the Arctic by Belding and his co-workers (1946). Clothing insulation must be reduced during activity in any environment; shedding garments is the obvious method, but in cold climates the Scandinavian "Brinje" system is useful; here the undergarment is thick but of very open mesh, the top garment is impermeable and closed during rest by a "zip" or other rapid fastening converting the open mesh into closed air cells. At rest these cells give excellent insulation; during activity the top garment is opened and sweat can evaporate freely through wide mesh to the outside air.

Electrically heated clothing or blankets are useful, but the heat produced must be enough, not only to give local warming but also to cover any extra heat loss due to that warming. The locally applied heat causes a reflex vasodilatation, so that heat loss from the body itself may be increased, and unless the heaters are adequate to cover this the individual will lose heat more rapidly than he can produce it, and will cool off internally; he then has a warm skin but suffers from "deep cold". This was experienced by air crews flying at high altitudes during the war. The possibility that an individual may be superficially warm but actually cold in his deep tissues must be remembered when treating cases of cold exposure. The closest indication to the deep tissue temperature is probably the rectal temperature.

gradient is lengthened and so the actual skin temperature is raised, thus giving the more equable micro-climate, whilst the surface temperature of the clothing is lower than the skin temperature would be. The total effect is to shift the comfort zone downwards, so that a clothed man sweats sooner than a naked man, and to postpone skin cooling, thus extending the zone of vasomotor control, and preventing early body cooling.

The insulating power of a fabric depends more upon the weave than upon the substance of which it is woven. A loosely woven thick fabric with plenty of air spaces within it will give more insulation than a tightly woven thin fabric of the same weight. Also the more layers of clothing there are, for a given weight of clothes, the better the insulation, because of the air between the layers. This is especially important in bed-making: the warmth of several blankets depends very much upon the air trapped between them; unless the blankets are separated and fluffed up frequently this air is squeezed out; the sleeper then feels the weight of the blankets, but complains that they have lost their warmth.

The continuous evaporation of the insensible perspiration makes it important that the clothing should be freely permeable to water vapour, that is, it should be "ventile". The effect of wearing non-ventile clothing is seen when wearing a rubber waterproof on a warm day. When there is a waterproof sheet in a bed anything between the body and this sheet may become damp with condensed insensible perspiration; therefore only a draw-sheet should be placed over the waterproof, and this should be moved round often to prevent its becoming damp. A waterproof sheet should never be placed between mattress and bedspring; water vapour from the body diffuses through the mattress and condenses on the waterproof; in a few days this condensation is sufficient to make the mattress quite wet, and the sleeper most uncomfortable. A similar effect is the moist patch on the inside of a groundsheet after a night sleeping on the ground; unless campers' bed-clothes are aired daily they soon become damp right through. An easy test for ventility is to blow through the fabric; if it is possible to blow through at all it will be sufficiently ventile. A fabric may be ventile but have been so treated as to be water repellent, so that liquid water will not pass through it; when the individual is not sweating this does not matter, but if he does sweat, any unevaporated perspiration, and there is always some, instead of gradually seeping through to the outside, will remain and saturate his undergarments, causing unnecessary discomfort.

Clothing needs to be loosely fitting with air spaces between the underclothes and the skin, and between the various layers. Underclothes should be light weight and loosely woven, but the top garments should be more tightly woven the better to keep in the imprisoned air beneath. Tight-fitting, thoroughly felted, old woollen underwear may be good for morale in cold weather, but does little to keep the wearer warm. Underclothes should be moderately absorbent, but not to the extent of getting really damp; for every gramme of water absorbed within the clothing from the insensible

perspiration, 590 calories of heat are saved by the system (body+clothes), but soggy clothes are not good insulators so more heat may be lost by conduction and convection later.

OUTDOOR CLOTHING AND PROTECTION AGAINST COLD

The same considerations apply for outdoor clothing as for indoors, but there are two points to be remembered. First, the more clothes worn the bulkier is the clothed body; this not only makes activity more difficult, but also increases the surface area, even ordinary clothes increase it by 16 per cent.; this tends to increase heat losses by conduction, convection and radiation. For any given environment there is an optimum thickness of clothing beyond which the disadvantage of increasing the surface area outweighs the gain in insulation. This particularly applies to gloves, sleeves and leg coverings, where the part protected is relatively thin; fingerless gloves can be made thicker than gloves with fingers, and sleeping bags thicker than trouser legs. The same problem is familiar to engineers lagging boilers and steam pipes.

The second point is activity: a thickness of clothing sufficient to keep an inactive man warm will be excessive as soon as he starts to work; metabolic heat will be retained within his clothes and soon conditions will be reached when he begins to sweat. If the water vapour from the evaporation of the sweat can diffuse through to the outside, this is only uncomfortable, but if there is such a thickness of clothing that condensation takes place in the more superficial layers, body cooling fails and there is danger of heat exhaustion. This problem has been examined in detail for the Arctic by Belding and his co-workers (1946). Clothing insulation must be reduced during activity in any environment; shedding garments is the obvious method, but in cold climates the Scandinavian "Brinje" system is useful; here the undergarment is thick but of very open mesh, the top garment is impermeable and closed during rest by a "zip" or other rapid fastening converting the open mesh into closed air cells. At rest these cells give excellent insulation; during activity the top garment is opened and sweat can evaporate freely through wide mesh to the outside air.

Electrically heated clothing or blankets are useful, but the heat produced must be enough, not only to give local warming but also to cover any extra heat loss due to that warming. The locally applied heat causes a reflex vasodilatation, so that heat loss from the body itself may be increased, and unless the heaters are adequate to cover this the individual will lose heat more rapidly than he can produce it, and will cool off internally; he then has a warm skin but suffers from "deep cold". This was experienced by air crews flying at high altitudes during the war. The possibility that an individual may be superficially warm but actually cold in his deep tissues must be remembered when treating cases of cold exposure. The closest indication to the deep tissue temperature is probably the rectal temperature.

CHOICE OF INDOOR CLIMATE

The acceptable indoor climate depends primarily upon the clothing. Americans wear lighter clothes than Britons and accordingly prefer a warmer indoor climate than we do.

Yaglogou and Messer (1941) showed that the preference by women for higher environmental temperatures was due to their wearing lighter clothes than men; women dressed in men's clothes were comfortable at an air temperature 4°F . (2.2°C .) lower than when dressed in their own light-weight garments.

But there are other factors to be considered: activity, which lowers the required temperature, and acclimatization. A given cool environment feels colder in summer than in winter; this is partly due to contrast and to the fact that in summer lighter clothes are worn, but even when these factors are eliminated comfort standards are found to be higher in summer than in winter; there must therefore be an acclimatization effect.

For thermal comfort the combination of clothing and indoor climate should be such that, at the level of activity under consideration, the heat loss from the individual, in his particular state of acclimatization, should not exceed his total heat production, in spite of moderate generalized cutaneous vasodilatation and in the absence of any extra purely calorogenic metabolic activity; he should not require to sweat, nor should there be any change in the heat stored within the body. The possible combinations are limited only by the physical properties of clothing and the ease with which any particular indoor climate may be obtained. It is not possible to lay down, on a theoretical basis, any definite standard; an empirical approach is necessary. The clothing in any community is moderately uniform, and it is possible to determine statistically for that community the temperature range for subjective thermal comfort.

Bedford (1948) questioned 2000 individuals, mostly females, engaged in light factory work, on their thermal comfort, and correlated their answers with the environmental temperature measured at the same time. He gave numerical values to the various thermal sensations, (+) for warm and (—) for cold, and obtained statistical correlations between the comfort score and different scales of warmth. The correlation coefficient for comfort with dry bulb temperature was -0.48 ; the best correlation was with equivalent temperature, with a coefficient of -0.52 . Bedford found the comfort zone for this community was $60-68^{\circ}\text{F}$. ($15.5-20^{\circ}\text{C}$.) dry bulb temperature, $57-63^{\circ}\text{F}$. ($13.9-17.2^{\circ}\text{C}$.) effective temperature, and $58-66^{\circ}\text{F}$. ($14.4-18.9^{\circ}\text{C}$.) equivalent temperature.

The Egerton Committee on the "Heating and Ventilation of Dwellings" (1945) has accepted Bedford's figures and applies them generally to recommend the following indoor climates:—

For living rooms.—Equivalent temperature $62-66^{\circ}\text{F}$. ($16.7-18.9^{\circ}\text{C}$.), to be attained either by air temperature $58-62^{\circ}\text{F}$. ($14.4-16.7^{\circ}\text{C}$.) and radiation of 40 B.T.U. per sq. ft. per hour (this is the radiation intensity 6 ft. in front of an open coal fire), or by air temperature $63-67^{\circ}\text{F}$. ($17.2-19.4^{\circ}\text{C}$.) and a mean radiant (=mean surface) temperature of $66-70^{\circ}\text{F}$. ($18.8-21.1^{\circ}\text{C}$.).

For bedrooms.—Equivalent temperature $50-55^{\circ}\text{F}$. ($10-12.8^{\circ}\text{C}$.). The

ventilation rate should be about 600 cu. ft./hr. per person. In sick rooms and hospital wards the living room rather than the bedroom standard should be applied, otherwise the nurse and others not actually in bed will be uncomfortably chilly unless they wear additional clothing.

SPECIAL CONSIDERATIONS

Thermal comfort can be destroyed by cold in certain particular regions, especially the feet, the midriff and the small of the back, and Ebbecke (1946) described during the war a reflex whereby cold on the face and neck produced generalized vasoconstriction elsewhere and slowing of the heart; this justifies the use of "mufflers" and even of the old-fashioned "respirator", but the effect is, in fact, only important at temperatures at or below freezing. Cold in the midriff and back can usually be remedied by changes in the cut of the clothes. Cold feet are often the result of wet feet; heat loss by conduction is relatively rapid through sodden socks and wet shoes; if the socks are changed, even though the wet shoes are replaced, conduction loss is so reduced that the feet soon warm up. A person getting into bed with cold feet may continue to have cold feet for a long time, especially if he is restless, because as quickly as one area of the bedclothes is warmed the feet are moved to another cold area. For rapid warming of the feet a suitable micro-climate must be established and maintained around them; this can be done with a hot-water bottle, but the more efficient and physiological method is to wear woollen bedsocks.

Women have a wider comfort zone than men, as at higher temperatures their metabolism is reduced, whilst at low temperatures the thicker layer of subcutaneous fat, present in most women, gives extra insulation, so that in a cool environment a woman's skin may be 2°F . cooler than a man's and her heat loss 10 per cent. less. Children have a more labile vasomotor system than adults and so their zone of vasomotor control is wider, and not only is a child naturally more active than an adult, but also his basal metabolic rate is higher: the basal metabolic rate of a child of ten years is over 50 calories per sq. metre, whilst that of an adult is from 38 to 40 calories. Hence children are able to maintain thermal equilibrium, even when at rest, at lower environmental temperatures than adults. But in infants the basal metabolic rate is low and the heat-regulating centres are not properly developed, so that a baby's temperature may vary a degree or more for purely physical reasons.

Any factor that alters metabolic rate will alter the sensitivity to cold, especially when at rest; if the central body temperature remains the same, as surface area does not alter, if the metabolism is reduced, vasomotor adjustments to heat loss are required earlier, and if it is increased the comfort zone is set lower. In undernutrition, hypothyroidism, and Addison's disease the patient is therefore unduly sensitive to cold and requires warmer clothing. In hyperthyroidism, diabetes insipidus, leukæmia and polycythæmia (Best and Taylor, 1945) the metabolism is raised, so that the patient may feel hot when others are just comfortable.

Age reduces the metabolism: at seventy there is a 10 per cent. reduction; at ninety a 20 per cent. reduction. This in itself makes some difference to cold sensitivity, and also the old are less active than younger individuals; hence old people feel the cold acutely. Also the vasomotor system in old persons is somewhat sluggish in action, so that an old individual cannot adapt himself so rapidly to changes in environmental temperature. The first line of defence against the cold in the old should be warm clothing, giving a stable micro-climate, rather than a warm indoor climate which is variable.

The heat-regulating centres are depressed in fatigue; fatal chilling is more likely to occur in an exhausted individual. The centres are also depressed during sleep and in anæsthesia. Heat loss is increased in venous obstruction, as the blood remains longer in the skin and subcutaneous tissues; on the other hand the metabolism is increased in cardio-renal disease.

An individual lying down on a cold conducting surface, such as stone or metal, loses heat rapidly by conduction, as the area in contact with the conducting surface is nearly half the surface area of the body. For this reason accident victims should never be laid direct on the pavement, but always on a coat or rug, to provide some insulation; and this is why it is always so important to have the metal top of a theatre trolley or operating table well protected with blankets, especially when the patient is under a general anæsthetic. A person in bed, however, is in an insulated space, with mattress below and bedclothes above; unless his metabolism is very low and his circulation is poor, as in shock, the whole space quickly reaches a point towards the upper limit of the comfort zone.

References

- Bazett, H. C. (1938): *J. Amer. med. Ass.*, **III**, 1841.
 Bedford, T. (1948): "Basic Principles of Ventilation and Heating", London.
 Belding, H. S., Russell, H. D., and Darling, R. C. (1946): *Fed. Proc.*, **5**, 7, and personal communication.
 Best, C. H., and Taylor, N. B. (1945): "Physiological Basis of Medical Practice", 4th edition, London, p. 536.
 Dufton, A. F. (1936): *J. Instn. Heat. Vent. Engrs.*, *Lond.*, **4**, 227.
 Dunham, W., Holling, H. E., Ladell, W. S. S., *et al.* (1946): "The Effects of Air Movement in Severe Heat", mimeographed report to the Medical Research Council, Number R.N.P. 46/316, H.S. 152.
 Ebbecke, C. (1946): personal communication, *quoted by* Ladell, W. S. S. (1946) in "A Visit to Germany to investigate certain War-time Advances in Applied Physiology", B.I.O.S. Final report No. 566, London: British Intelligence Objectives Subcommittee.
 Egerton Committee (1945): "Heating and Ventilation of Dwellings", Post-war building studies No. 19, London: H.M. Stationery Office.
 Houghton, F. C., and Yaglogou, C. P. (1923): *Trans. Amer. Soc. Heat Vent. Engrs.*, **29**, 165.
 —, — (1924): *Ibid.*, **30**, 193.
 Ladell, W. S. S. (1947): *Brit. med. Bull.*, **5**, 5.
 Markham, S. F. (1947): "Climate and Energy of Nations", London.
 Molnar, G. W. (1946): *J. Amer. med. Ass.*, **131**, 1046.
 Yaglogou, C. P., and Messer, A. (1941): *Ibid.*, **117**, 1261.

CURRENT THERAPEUTICS

XX.—AUREOMYCIN AND CHLOROMYCETIN

By LIEUT.-COLONEL W. H. HARGREAVES, O.B.E., M.R.C.P., R.A.M.C.
Lately British Medical Liaison Officer, the Office of the Surgeon General, United States Army.

THE rapid establishment of these antibiotics has been followed with great interest from this side of the Atlantic, and almost weekly there comes additional proof of their usefulness in a wide variety of infections. In America, many thousands of actinomycetes from soil samples obtained from various parts of the world have been investigated for possible antibacterial properties. This search is still continuing, and the three most important discoveries so far have been streptomycin, chloromycetin and aureomycin. Chloromycetin was obtained in 1947 from a new species of streptomyces obtained by Doctor Paul Burkholder at Yale University from a soil sample which came from a mulched field in Venezuela. The active compound was isolated in pure crystalline form in the laboratories of Parke, Davis and Company at Detroit, and this year its synthesis has been announced. Aureomycin was isolated in 1948 at Lederle Laboratories in New York. It is a yellow crystalline antibiotic obtained from a strain of *Streptomyces aureofaciens*. Ease of administration is one of the most outstanding advantages of both these drugs, for they exert a satisfactory systemic action when given by the mouth. Again, many hundreds of patients have been treated with them and there has been no significant evidence of clinical toxicity up to the present. In the case of aureomycin, patients sometimes experience nausea and there have been instances of vomiting, but these symptoms have not persisted. Both drugs suppress the flora in the intestinal tract, so that if prolonged treatment is ever necessary the patient should be given vitamin supplements. Aureomycin may produce a greenish discoloration of the urine.

RANGE OF ACTIVITY

Both aureomycin and chloromycetin exert a powerful action in rickettsial infections and against viruses of the psittacosis-lymphogranuloma group. They are antagonistic also to a wide range of bacteria. Broadly speaking, aureomycin is more versatile, for whilst they both exert a comparable effect against most gram-negative organisms, aureomycin is superior against gram-positive organisms. Both are effective *in vitro* against organisms of the *Brucella* group, *B. tularensis*, *H. pertussis*, certain spirochaetes, and some strains of *Mycobacterium tuberculosis*. Experimental infections of mice with cholera respond to chloromycetin.

Resistance *in vitro* to aureomycin has been produced with difficulty in

August 1949. Vol. 163 (153)

some organisms. So far, there have been no reports of organisms becoming resistant to chloromycetin. Up to the present, the reported clinical trials with aureomycin have covered a wider range of infections than those with chloromycetin.

RICKETTSIAL AND VIRUS DISEASES

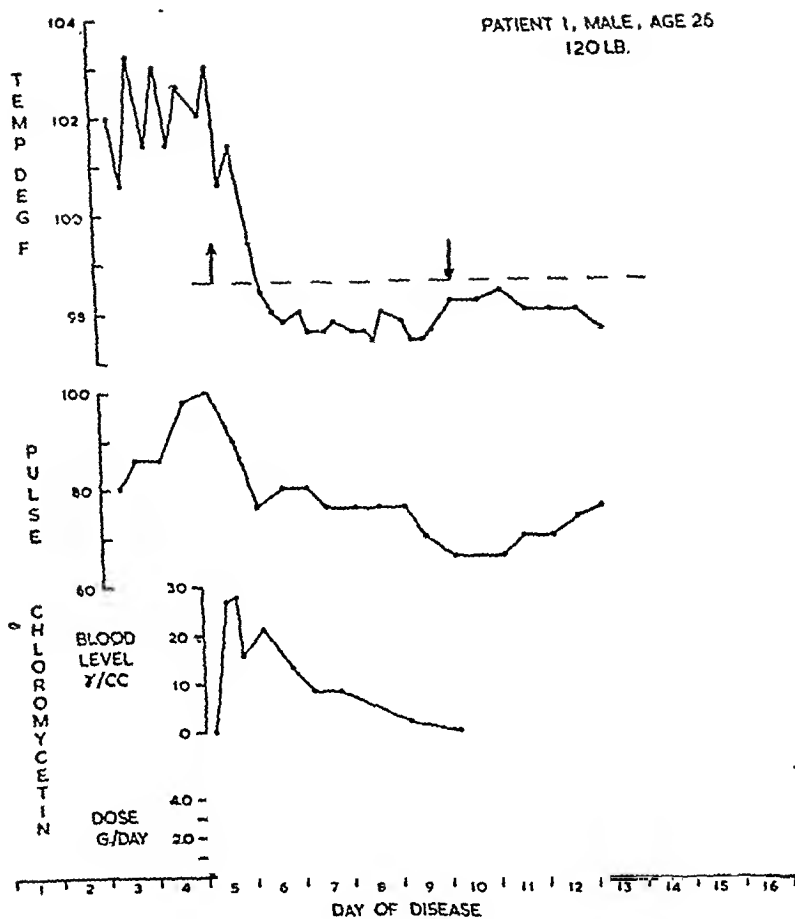
Following laboratory investigations which showed that chloromycetin had a specific action in rickettsial infections, and after the drug had been found to be non-toxic when given to human volunteers, the first clinical trials were undertaken in cases of *typhus fever* (Smadel and Leon, *et al.*, 1948; Payne *et al.*, 1948). The response of these cases was most encouraging and the next step in the clinical testing of chloromycetin came when Smadel and his team from the Army Medical Centre, Washington, D.C., flew to Malaya. There, with the members of the Institute for Medical Research at Kuala Lumpur, they treated a controlled series of 25 patients with *scrub typhus* (Smadel and Woodward, *et al.*, 1948). The results were dramatic, and figure 1 presents the findings in the first patient to be treated.

On an average, treatment was begun on the sixth day of the fever and the temperature became normal after an average of thirty-one hours. Among 12 untreated cases the duration of fever averaged eighteen days. In the treated cases there were no deaths and no complications, whereas among the controls one developed parotitis and in another pneumonia occurred and the patient died on the seventeenth day. In the early cases of the series chloromycetin was given for several days, but during the course of the work it was found possible to reduce the length of treatment and the last 7 patients received the drug for twenty-four hours only—a total of 6 g. by mouth—and responded equally well. The current practice is to give an initial dose of 4 g. and to follow this with approximately 0.25 g. by mouth, every two to four hours for four or more doses. It seems possible that as more and more cases are treated this regime may be modified further.

Chloromycetin was next tried in another rickettsial disease, *Rocky Mountain spotted fever* (Pincoffs *et al.*, 1948). The Eastern form is endemic in Maryland, where the vector is the dogstick, *Dermacentor variabilis*: 15 proved cases of this form of the disease were treated, and here again the results showed chloromycetin to be an effective therapeutic agent.

Aureomycin has also proved effective in experimental rickettsial infections, but as yet its clinical tests in this field have not been as thorough as those with chloromycetin. The small number of cases of Rocky Mountain spotted fever and typhus fever so far treated have responded satisfactorily, and comparative clinical trials between the two antibiotics should prove important. Meanwhile, a series of cases of *Q fever* have been treated with oral aureomycin (Lennette, Meiklejohn and Thelen, 1948): 14 acutely ill patients responded promptly, and in one chronic case the drug was disappointing.

Both aureomycin and chloromycetin are effective in experimental infections with the virus-like organism of *lymphogranuloma venereum*. Aureomycin has been used successfully in a series of 25 human cases. This drug



RASH	+++	++	+	0	0														
ESCHAR	+	+	+	+	+	+	±	0											
B.P.						104/70	100/70	99/73	104/70	99/70	104/70	110/70	112/74						
WBC (THOUSANDS)									60										72
RBC (MILLIONS)									40										42
WF OX-K			80				320		1280			5120							5120
RICKETTSÆMIA	+	+	+	0															

Fig. 1.—Chloromycetin in scrub typhus.

Reproduced from *Boletín de la Oficina Sanitaria Panamericana*, 28, 1 (Smadel, 1949).

Chloromycetin also is stated by Parke, Davis & Co. to have been used successfully in several cases of primary atypical pneumonia, but up to the present no report has been published.

BACTERIAL INFECTIONS

Typhoid fever.—During the course of the work with chloromycetin in scrub typhus last year numerous cases of typhoid fever were encountered. The drug had been shown to be active against gram-negative bacteria, so these cases of typhoid fever, which tends to run a severe course in Malaya, presented a great opportunity for a clinical trial (Woodward, Smadel, *et al.*, 1948).

Ten cases were treated, all confirmed by positive blood cultures. Chloromycetin was given orally—an initial dose of 50 mg. per kg. of body weight followed by 0.25 g. every two hours until the temperature was normal, and subsequently 0.25 g. every three to four hours for five days. The total dosage averaged 19.1 g. over a period of 8.1 days. The cases treated were all in the first two weeks of their fever and clinical improvement was usually evident within twenty-four hours. The average duration of fever after the treatment was started was 3.5 days. In 8 cases daily

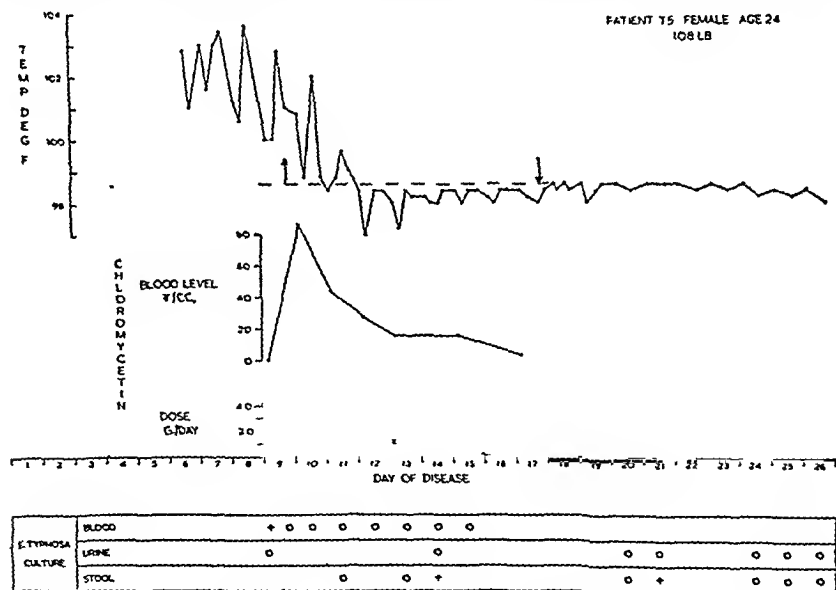


Fig. 3.—Chloromycetin in typhoid fever.

Reproduced from *Annals of Internal Medicine*, 29, 131 (Woodward *et al.*, 1948).

blood cultures were taken for the first five days of treatment and all of these cultures were sterile. No patient was discharged without three negative stool cultures having been obtained. The progress of an average case is shown in figure 3. Intestinal perforation occurred in one case and in another there was a massive intestinal hæmorrhage. These both recovered, the former being given streptomycin and penicillin in addition to chloromycetin and the latter being transfused. Two cases

relapsed with positive blood cultures after afebrile periods of ten and sixteen days; they both responded to second courses of chloromycetin, and when the organisms were tested *in vitro* they showed no loss of sensitivity to the drug. In a control series of 8 cases, one died on the seventeenth day and the average duration of fever in the remaining 7 cases was thirty-five days.

There is every reason to believe that these extremely encouraging results with chloromycetin will be confirmed by investigations carried out during a recent outbreak of typhoid fever in England (Bradley, 1949). Meanwhile, aureomycin has so far proved disappointing in the treatment of this disease, but it may be effective in large doses and further research is in progress.

Brucellosis.—Both antibiotics have a bacteriostatic action against brucellæ, and they have both been used with success in acute cases of brucellosis. In the Middle West of America, where this disease has been a great problem for years, the immediate therapeutic results with aureomycin at the University of Minnesota were found to surpass those from any previous line of treatment, including streptomycin and sulphadiazine in combination (Spink *et al.*, 1948). At the Mayo Clinic, experiments have been carried out with controlled series of mice inoculated intraperitoneally with *Br. suis* and *Br. abortus* (Heilman, 1949). Various drugs, separately and in combination, were administered to these infected mice and they were killed on the day after treatment was stopped. Their spleens were removed and the number of organisms per spleen was estimated after a process involving freezing, thawing, emulsification, dilution and culture. The best results were given by aureomycin combined with streptomycin, although even this combination did not eliminate all the organisms. Neither aureomycin nor chloromycetin was particularly effective when given alone, but of the two, aureomycin was superior.

The combined use of aureomycin and dihydrostreptomycin has been tried in four patients, two with *Br. suis* and two with *Br. abortus* infections, with satisfactory results (Herrell and Barber, 1949). The recommended line of treatment is: aureomycin, 3 g. daily by mouth, combined with dihydrostreptomycin, 2 g. per day intramuscularly, for twelve to fourteen days in acute cases and for twenty-one to twenty-eight days in chronic cases. Lederle Laboratories Division report that Herxheimer-like reactions have occurred with aureomycin in the preliminary clinical studies with brucellosis. They state that if the dosage for the first two or three days is kept down to 250 mg. to 500 mg. daily the incidence of undesirable side-reactions is decreased.

Tularæmia.—Rabbit fever, which is rarely diagnosed in Britain, is comparatively common in America. Before streptomycin was found to be specific for this infection the typhoidal type often proved fatal. In a recent investigation the effectiveness of streptomycin, aureomycin and chloromycetin have been compared in the treatment of controlled series of infected mice (Woodward, Raby, *et al.*, 1949). In these tests aureomycin was found to be more effective than streptomycin, whilst chloromycetin was

disappointing. Subsequently, three patients who were seriously ill with the typhoidal type of tularæmia were treated with aureomycin by mouth. They all responded satisfactorily and the clinical effect of the drug was considered comparable to that of streptomycin.

Infections caused by gram-positive cocci.—Comparisons of aureomycin, chloromycetin and penicillin *in vitro* have shown that aureomycin is from four to sixteen times as active as chloromycetin against streptococci, pneumococci and staphylococci, but much less active than penicillin, with some important exceptions. This work by Long *et al.* (1949) is summarized in the following table :—

COMPARISON OF CHLOROMYCETIN, AUREOMYCIN, PENICILLIN G *in vitro*

GRAM-POSITIVE COCCI					Minimal Inhibitory Concentration (Gamma ml.)		
Organism					Chloro.	Aureo.	Peni. G
<i>Streptococci:</i>							
<i>Beta group</i>	A	C203	5	0.312	0.008
	B	090	5	1.25	0.016
	B	19	5	0.625	0.035
	C	K61	5	0.625	0.016
	D	Zymo.	10	1.25	2.5
	D	22A	10	0.625	2.5
	F	For.	2.5	0.625	0.05
	F	H59	5	1.25	0.016
<i>Alpha faecalis</i>	Bl.	10	1.25	2.5
	Tar.	10	1.25	2.5
	West.	10	1.25	2.5
<i>Viridans</i>	Dop.	5	0.625	0.625
	Keel.	10	0.625	2.5
<i>Pneumococcus</i>	I	SVI	2.5	0.312	0.016
<i>Staphylococci:</i>							
<i>Aureus</i>	Zeut.	5	0.625	0.062
	Zorn.	5	0.625	0.062
	Gelb.	5	0.625	0.062
	Gibb.	10	0.625	0.012
<i>Albus</i>	Heatly	5	0.625	0.012

Aureomycin proved effective in several cases of severe staphylococcal infection with bacteriæmia which had not responded to sulphadiazine and/or penicillin. One patient with *Strep. faecalis* meningitis and another with subacute bacterial endocarditis caused by this organism were cured by oral aureomycin. Prompt recovery is reported in a case of pneumococcal meningitis in which the infecting organism had become resistant to sulphadiazine and penicillin.

Infections caused by gram-negative cocci.—Sixty-six cases of gonococcal urethritis have been treated with aureomycin with results which were satisfactory but not as good as could be expected with penicillin (Finland,

Collins and Paine, 1948). One case of meningococcal bacteraemia has been cured with aureomycin (Collins, Paine and Finland, 1948). As yet, there have been no published reports regarding the use of chloromycetin in these infections.

Infections of the urinary tract.—Both antibiotics are useful in clearing coliform infections of the urinary tract. The immediate effects have been satisfactory but, of course, more time must elapse before their value in this field can be assessed. The early results with aureomycin in mixed infections with *E. coli*, *A. aerogenes* and *Strep. faecalis* have been promising. Chloromycetin is relatively effective *in vitro* against certain strains of *Proteus vulgaris*, but neither drug has shown any significant activity against *Ps. aeruginosa* (*pyocyanea*) compared with polymyxin D (Long *et al.*, 1949).

Ocular infections.—Aureomycin borate is successful in 0.5 per cent. concentration when applied locally in cases of conjunctivitis due to staphylococci, pneumococci, *H. influenzae*, Friedlander's bacillus and the Morax-Axenfeld diplococcus (Braley and Sanders, 1948). Some virus-like infections also respond to the drug; inclusion conjunctivitis, follicular conjunctivitis and herpes simplex of the cornea.

SPIROCHÆTAL INFECTIONS

Both drugs are active *in vitro* against spirochætes of relapsing fever, and aureomycin has been used successfully in the treatment of experimental relapsing fever in mice and Weil's disease in hamsters (Heilman, 1948). In the treatment of these two experimental infections aureomycin is more effective weight for weight than penicillin.

Syphilis.—O'Leary, Kierland and Herrell at the Mayo Clinic have carried out preliminary clinical trials of oral aureomycin in syphilis with very encouraging results. In December 1948 they described the response of two cases with primary lesions which were dark-ground positive. *Treponema pallidum* disappeared promptly from the chancres, which healed satisfactorily. Both cases became serologically negative and subsequently have shown no evidence of relapse (O'Leary, Kierland and Herrell, 1948). In addition, 2 further patients with late nodulo-ulcerative lesions of syphilis have healed clinically, and aureomycin has been given by mouth to patients with various types of neurosyphilis. Here there has been a rapid decrease in the pleocytosis, with less marked and less rapid reversal in the other findings in the cerebrospinal fluid. A great deal more work is necessary to decide on the dosage and duration of treatment and on the advisability of combining intramuscular penicillin with oral aureomycin.

PREPARATIONS

Aureomycin hydrochloride (Lederle) is available in capsules of 25, 50 and 250 mg. Troches are made containing 15 mg. of the drug, designed to be

dissolved in the mouth in cases of bacterial infections of the mouth and throat. Vials of 25 mg. aureomycin mixed with 25 mg. sodium borate and 62.5 mg. sodium chloride are available for ophthalmic use. The solution is prepared by adding 5 ml. of distilled water, and it will remain stable for about two days if kept in a refrigerator. *Aureomycin hydrochloride ointment* is produced in tubes of 1 ounce. It contains 3 per cent. by weight of aureomycin and is designed for topical application.

Chloromycetin ("chloramphenicol": Parke, Davis) is supplied in capsules containing 0.25 g.

CONCLUSION

Aureomycin and chloromycetin are both available in Britain now, but supplies are limited and they are very costly. It is expected that this situation will improve before long. An attempt has been made here to review their scope as it is known at the present time. The full possibilities of these very important antibiotics have still to be explored and the correct dosages for different infections have yet to be decided.

References

- Bradley, W. H. (1949): *Lancet*, i, 869.
 Braley, A. E., and Sanders, M. (1948): *J. Amer. med. Ass.*, 138, 426.
 Collins, H. S., Paine, Jun., T. F., and Finland, M. (1948): *Proc. Soc. exp. Biol.*, N.Y., 69, 263.
 Finland, M., Collins, H. S., and Paine, Jun., T. F. (1948): *J. Amer. med. Ass.*, 138, 946.
 Heilman, F. R. (1948): *Proc. Mayo Clin.*, 23, 569.
 — (1949): *Ibid.*, 24, 133.
 Herrell, W. E., and Barber, T. E. (1949): *Ibid.*, 24, 138.
 Kneeland, Y., Rose, H. M., and Gibson, C. D. (1949): *Amer. J. Med.*, 6, 41.
 Lennette, E. H., Meiklejohn, G., and Thelen, H. M. (1948): *Ann. N.Y. Acad. Sci.*, 51, 331.
 Long, P. H., Schoenbach, E. B., et al. (1949): *Calif. Med.*, 70, 157.
 Meiklejohn, G., and Shragg, R. I. (1949): *J. Amer. med. Ass.*, 140, 391.
 O'Leary, P. A., Kierland, R. R., and Herrell, W. E. (1948): *Proc. Mayo Clin.*, 23, 574.
 —, —, — (1949): *Ibid.*, 24, 302.
 Payne, E. H., Sharp, E. A., and Knaut, J. A. (1948): *Trans. R. Soc. trop. Med. Hyg.*, 42, 163.
 Pincoffs, M. C., et al. (1948): *Ann. intern. Med.*, 29, 656.
 Smadel, J. E. (1949): *Bol. Ofic. san. Panamer.*, 28, 1.
 —, Leon, A. P., et al. (1948): *Proc. Soc. exp. Biol.*, N.Y., 68, 12.
 —, Woodward, T. E., et al. (1948): *Science*, 108, 160.
 Spink, W. W., Braude, A. I., Castaneda, M. R., and Goytia, R. S. (1948): *J. Amer. med. Ass.*, 138, 1145.
 Woodward, T. E., Raby, W. T., et al. (1949): *J. Amer. med. Ass.*, 139, 830.
 —, Smadel, J. E., et al. (1948): *Ann. intern. Med.*, 29, 131.
 Wright, L. T., et al. (1948): *Ann. N.Y. Acad. Sci.*, 51, 318.

REVISION CORNER

THE DIFFERENTIAL DIAGNOSIS OF PALPITATION

By palpitation is meant consciousness on the part of the subject of the beating of his own heart. The word comes from the Latin *palpitare*, to throb. The purpose of this short article is not to adduce a long list of lesions which may at times cause palpitation, but to emphasize that although such causes are legion the symptom is almost always a harmless one, and only exceptionally a sign of serious heart disease. To this end the following clinical classification is suggested:—

- (1) No disease whatsoever is present. This is by far the largest group.
- (2) Disease other than of the heart is present. This group accounts for most of the remaining patients.
- (3) Cardiac disease is present. This is a most uncommon group, and even here it is distinctly unusual for palpitation to be the presenting symptom in a patient suffering from cardiac disease.

NO ORGANIC DISEASE

J. C. Williams of Edinburgh, over a century ago, clearly recognized the frequent absence of disease in cases of palpitation, as is shown by the title of his book "Practical Observations on Nervous and Sympathetic Palpitation of the Heart, Particularly as Distinguished from Palpitation the Result of Organic Disease" (1836). In sensitive individuals consciousness of the heart beat may arise from physiological causes such as exertion, and as a result of a sudden fright. It is common during convalescence from any debilitating disease. The sensation is commonly described as being rather unpleasant, but it is never associated with pain. There may be no disturbance of cardiac rhythm present, or if an arrhythmia is responsible for it, it is an unimportant one such as extrasystoles or supraventricular paroxysmal tachycardia. This type of palpitation may occur when the patient is worried, and is apt to be troublesome when the subject is just falling off to sleep. The patient with extrasystoles may complain that his heart stands still, or he may be conscious only of the forceful contraction following the pause. Similarly, the patient may be conscious only of the onset or offset of a bout of paroxysmal tachycardia. It is not yet sufficiently widely appreciated that paroxysmal tachycardia, after extrasystoles, is the most common arrhythmia, and that the supraventricular type, which is so much commoner than the ventricular variety, is only exceptionally the result of heart disease. Often no cause is discoverable and the outlook is excellent. Excessive smoking and over-indulgence in tea or coffee may give rise to palpitation, and a simple tachycardia is usually found. Alcoholic excess may lead to palpitation, and it is being increasingly recognized that this may be due to a transient bout of auricular fibrillation. Samuel Levine recently discovered a few such cases among internes!

NON-CARDIAC DISEASE

By far the most common of these conditions is the effort syndrome. This is best regarded as one of the many facets of an anxiety state. Its synonym of "irritable heart" is a poor one—it is the patient who is irritable. Sometimes the palpitation is associated with a stabbing pain beneath the left breast.

Of the organic diseases, flatulent indigestion heads the list. Broadbent's advice was that when a patient complains of the heart, examination of the stomach should be made; and, of course, examination of the gall-bladder must not be omitted in such a case. Anæmia of any severity is commonly accompanied by palpitation. This is closely associated with exertion and may, in fact, be the presenting symptom.

Pulmonary tuberculosis, with or without anæmia, may also present in this manner. Masked thyrotoxicosis also must always be carefully excluded. This is particularly so if auricular fibrillation without obvious cause is present; but simple tachycardia may be sufficient. The diagnosis of thyrotoxicosis is suggested if extrasystoles occur together with tachycardia. Any condition embarrassing the heart by local pressure, such as a pneumothorax or pleural effusion, or tympanites, ascites or even pregnancy, may result in palpitation. Palpitation is very common during the sudden hypertensive crises due to the outpouring of adrenaline from the rare phæochromocytoma of the medulla of the suprarenal. Because it is accompanied by tremor and sweating it may easily be attributed to an anxiety state, but commonly there is also migrainous headache, and sometimes anginal pain appears.

CARDIAC DISEASE

So rarely does a patient with heart disease give palpitation as the main complaint that in any case offering it as such it is almost an assurance that the heart is healthy! Nevertheless, patients with auricular fibrillation do occasionally complain of palpitation and in a few of these the sensation can be extremely unpleasant. Auricular flutter, with or without a varying block, may cause similar symptoms and an electrocardiogram is often required to distinguish it from auricular fibrillation. Heart block is another rare cause, and the patient may complain that his heart beats too slowly and too forcibly, although it is more common for him to be aware of occasional dropped beats. Again, it is the sensitiveness of the patient that counts and not the degree of slowness of the heart or the number of beats dropped. Very rarely, the hypertensive patient will complain of "pounding" in his chest and head, and the patient with a free aortic reflux may do so. Following lumbo-dorsal sympathectomy for hypertension, palpitation may be associated with the transient postural hypotension.

TREATMENT

From what has been said regarding the etiology of palpitation it follows that a complete physical examination is required in every case. Although in the majority of cases no disease will be discovered, its reassurance value to the patient is without equal. A simple explanation of his symptom is then all that is required. The administration of sedatives is to some extent an admission of defeat, but it may be justified for a short time, perhaps to help tide the patient over a period of particular stress. With a frank anxiety state it may be advisable to seek the help of a psychiatrist.

Extrasystoles are a common cause of the patient's discomfort and they can usually be regarded as, to use Wenckebach's phrase, "harmless nonsense of the heart". Unfortunately, at times they may result from serious heart disease, and it is for this reason that it is recommended that an electrocardiogram be taken. In health the form of an extrasystole remains remarkably constant for many years, down to the smallest notch. In disease, ventricular extrasystoles may be variform, or they may alternate in shape and direction. Sometimes a hint that cardiac infarction has occurred may be gained from their appearance. Rarely, after a bout of extrasystoles, the diseased ventricle may show transient electrical alternation of the QRS complexes or, still more rarely, of the T waves. Even if extrasystoles are the result of cardiac disease, the decision whether or not to use quinidine for the prevention of this type of palpitation is not easy. I am of the opinion that it should not be employed without some definite indication, and three types of patient fall within this category. The most definite of these is the patient who develops numerous ventricular extrasystoles following cardiac infarction. Here quinidine is given, not so much to abolish palpitation but with the object of preventing the onset of ventricular tachycardia or ventricular fibrillation. Another instance, although rare, is the non-

neurotic patient who is experiencing such frequent extrasystoles that they are causing giddiness and faintness. Finally, in a patient known to have mitral stenosis, the appearance of auricular extrasystoles sometimes presages auricular fibrillation. In such a case quinidine may be given in the hope of postponing fibrillation.

SAMUEL ORAM, M.D., F.R.C.P.

THE TREATMENT OF BOILS

A BOIL, or furuncle, begins as a staphylococcal infection of a hair follicle or sweat gland. The organisms, having effected an entrance, spread to a varying extent into the surrounding subcutaneous tissues before they are localized by a barrier of leucocytes, mobilized by the local inflammatory reaction. Suppuration occurs within the encircling defensive zone and the boil subsequently bursts to the surface of the skin to discharge pus and its "core", the latter consisting of that part of the tissue battle-ground which has suffered to the point of necrosis. The vast majority of boils remain localized inflammations, but serious metastatic complications do occasionally arise.

Treatment involves consideration both of the local lesion and of the patient as a whole. To consider the latter first: most sufferers from boils seem to be predisposed to staphylococcal infections without there being any apparent reason; but any generalized cause of ill health, e.g., a deficient diet, prolonged overwork or debilitating diseases, will predispose a normally resistant person to invasion by the staphylococcus. It is mortifying to overlook, amid the minutiae of local treatment, diabetes or chronic nephritis, sufferers from both of which conditions are particularly liable to boils. It is clearly of greater importance to remedy underlying causes than to attend to the local manifestations of any disease, and the patient with boils is no exception to the rule that a sick man should be regarded as an entire person and not as a symptom.

There are local predisposing causes for boils. The neck, the forearms and the axillæ, favourite sites for recurrent boils, may be chafed by sweat-soaked and infected clothing. Clean clothes, avoidance of chafe, and a dry skin are desirable as discouraging to bacterial multiplication and spread.

GENERAL TREATMENT

A man with a single small boil is unlikely to need or to submit to any alteration of his daily routine. But recurrent boils require that his diet be overhauled to see that it contains as much protein- and vitamin-containing foods as is possible in these difficult days and that it is not overweighed with carbohydrates. A congenial holiday is a recommendation often regarded as Utopian and impracticable, but its value is great. General ultra-violet light and injections of staphylococcus toxoid seem both to be useful in raising the body's general resistance to staphylococci, but it is doubtful whether there are any other useful methods of doing this, despite the claims of numberless preparations and treatments.

LOCAL TREATMENT

The aim of local treatment is to raise the efficiency of the local defence mechanisms, or to weaken the invading bacteria, or to combine both.

Rest is essential to local resistance. It is most commonly and most abruptly interrupted by the patient or a nurse giving the inflamed area "a good squeeze". The squeezing of boils is always a mistake and has, on occasions, proved to be a fatal error. Rest can be obtained in various ways, e.g., by providing a sling for those with boils on the arm; and a boil of any size is an indication for a patient to cease work so that the inflamed part can be rested.

The intensity of the local inflammatory reaction is increased by *heat*, which is

therefore useful. An infra-red lamp is the ideal method of applying it but a hot-water bottle on top of a kaolin poultice is usually more practicable. Hot boracic fomentations are an abomination—they remain hot for a very short time, are infrequently changed and are nearly always too wet. They macerate the skin without offering compensations for this assistance to the growth of bacteria. Heat may be applied in the form of hot soaks in a basin or hand-bath, or by the old expedient of bandaging some cotton-wool to the bowl of a wooden spoon, dipping it into a basin of hot water repeatedly charged from a kettle, and applying it to the boil. Such methods bring heat to the inflamed part without keeping it constantly moist. Hypertonic crystalloid solutions draw water out of exposed tissues by osmosis and may thus be made to promote a flow of fresh tissue fluid into an inflamed area. Intact skin offers a serious barrier to osmosis and such things as magnesium sulphate paste (which is too painful to be a welcome application), hypertonic saline, or 12½ per cent. sodium sulphate solution are much more useful after a boil has burst or been incised than before.

Incision.—The majority of boils do not need incision. In particular, incision must be avoided for boils of the face, nostrils and upper lip. There is no harm elsewhere in incising a boil if the skin over it is red and thin, but too early an incision is always worse than no incision at all. A small linear or cruciate incision, large enough only to evacuate pus and sloughs, is the most that is required and “if in doubt, don’t incise” is a good maxim. Dressings of dry gauze or *tulle gras* after operation can usefully alternate with hot soaks in hypertonic sodium sulphate solution. Packing should never be used—packs act more often as corks than as drains.

PENICILLIN THERAPY

The causative organisms of boils can usually be attacked by penicillin, but they are sometimes insensitive or relatively insensitive. Boils caused by the latter class of organism, if treated with penicillin, may come to resemble a fire in which the flames are quenched but the embers continue to smoulder. Such a state is much more tedious to patient and doctor than an acute infection. Occasionally, patients suffer severe allergic reactions from penicillin. For these reasons a single simple boil should not be treated with penicillin. If the boil is on the face, if it is large, if there are constitutional symptoms, or if it is the latest of a series, penicillin should be given by injection, 200,000 units twice daily for four or five days. Penicillin does nothing to raise a patient’s resistance to staphylococci and does not therefore guarantee against recurrence of boils. Local application of penicillin is of little value until a boil is open, and even then cannot reach the recesses of a cavity as effectively as it can *via* the blood, but it is sometimes useful as a cream to prevent the discharges from a boil in a moist situation (such as the axilla) from infecting neighbouring hair follicles.

R. S. HANDLEY, O.B.E., M.B., F.R.C.S.

ENEMAS

It is the evacuant type of enema which will be discussed in this article. There are certain retention enemas in use, but except possibly for starch and opium, which is a soothing symptomatic treatment for diarrhoea, they are not concerned here. Other retention enemas, such as nutrient enemas, have fallen into disuse as it is recognized that the nourishment is not absorbed. Water is the important substance freely absorbed by this route and is widely used in the form of “rectal saline”. It is best given as plain water, and large quantities of this life-saving fluid can be absorbed by this method when properly used. It is perhaps appropriate to mention here that the way to achieve this is to have a minimum and even pressure of fluid.

The rectal tube should be of good-sized bore (not less than $\frac{1}{2}$ inch) and should if possible be attached direct to a small funnel (3 to 4 ounce [85 to 115 ml.] capacity is convenient) containing about an ounce (28.5 ml.) of water. If any connexions are necessary in this part of the apparatus they must be of equal bore and not narrower. The funnel is arranged 1 to $1\frac{1}{2}$ feet only above the level of the anus, is open to atmospheric pressure, and is replenished from a large reservoir suspended above, from which the fluid drips slowly through a drip chamber into the funnel. If the patient coughs and the intra-abdominal and therefore intra-rectal pressure is raised, the fluid in the funnel can be seen to rise markedly. Even respiratory movement can be seen in the funnel fluid level, which demonstrates that no increased pressure can be corked up in the bowel when this method is used, and experience shows that using it makes the absorption of up to 9 pints (5 litres) or even more in twenty-four hours a practicable matter.

INDICATIONS FOR USE

Evacuation of the bowel may have to be assisted or ensured: (1) when constipation is present; (2) when it is wished to make an endoscopic examination of the bowel; (3) when an operation on the bowel is intended; and (4) when obstruction is suspected and information sought as to whether the lower bowel is being filled from above. In the first three groups the employment of either enemas or aperients may be considered; in the fourth group it is essential to avoid aperients and employ only enemas.

Experience shows that it is still necessary to continue emphasizing the grave risk of perforation if an aperient is given in the presence of *obstruction*. An enema, on the other hand, is both safe and informative. If no result is obtained the diagnosis of obstruction becomes probable; if there is a result with the first enema the administration of a second, one or two hours later, with no result will have the same significance. It is just worth bearing in mind that something depends upon the person administering the enema. An inadequate enema may not empty completely the bowel below an obstruction and a second will therefore still produce a result, whilst an over-enthusiastic enema may cause such a clearance that a patient with no obstruction may produce nothing with a second attack. The importance of such fallacies is relative only to the difficulty of diagnosis, and should not, of course, be taken too seriously when all other evidence points in one direction.

Whether or not an enema is used for *constipation* depends in part upon the degree. In an acute, severe case, for example, a patient with a fissure-in-ano, whose rectum has become choked up with hard faeces on account of the pain of evacuation, the more comfortable method of assistance is by enema (occasionally digital evacuation under anaesthetic is required). Oil run in by catheter overnight to soften the faeces, followed by gentle repeated washouts to break away small pieces at a time, is the kindest treatment. In chronic constipation from atony, commonly seen in the aged, and in cases of adult megacolon, it may be essential to use enemas, at least occasionally.

PREOPERATIVE BOWEL EVACUATION

For many operations purgation is not necessary, and is indeed a harmful disturbance. Preoperative enemas are therefore not now employed so extensively as previously, although it should be noted that the practice dies much harder among the nursing than the medical profession. Inquiry reveals surprisingly often that the most trivial and irrelevant cases are prepared in this way. When it is necessary to have an empty bowel, of course the matter is different. Resections of the large bowel are safest when the bowel is both out of use and empty. A preliminary colostomy ensures the former and washouts the latter. Such washouts are best carried out through and through from colostomy to rectum, but before this can be achieved rectal washouts may be necessary. It is not often that a wash-through cannot eventually be obtained, as the final completion of an obstruction is usually by a faecal plug in a narrowed lumen rather than complete obliteration of the lumen itself. Before such operations as hæmorrhoidectomy or sigmoidoscopy the choice between aperients and enemas

for clearing the field is a matter of individual preference. Some think that enemas may cause too much disturbance of the bowel, leading to an irritative diarrhoea which is anything but helpful; moreover, if any fluid has been retained it may be returned when the bowel is manipulated and this is equally trying. On the whole I am in favour of moderate aperients with sometimes a low rectal washout for hæmorrhoids, and often no preparation at all for sigmoidoscopy. If the view is obscured by fæces the examination is repeated after whatever preparation seems suited to the case.

CHOICE OF SUBSTANCE AND METHOD

Consideration needs to be given to the substances and methods used when enemas are ordered. There are two mechanisms whereby evacuation may be produced: chemical irritation by the substances dissolved in the fluid, or the physical pressure of the fluid itself. Both factors operate with the ordinary soap enema. Soap, however, is a very effective irritant and may cause a marked hyperæmia of the bowel as well as a painful tenesmus. Soft soap properly dissolved in not too great concentration minimizes these effects, but even so a little soap in the eye or up the nose demonstrates the irritation it can produce on mucous membranes. Many consider that its routine use should be discouraged. It is obviously undesirable to inflame the colon if the simple and natural method of raising the intra-luminal pressure will produce results. It is true that an obstinate case may not respond to a gentle slow raising of the pressure such as occurs when water is run in through a tube and funnel; but rather than add soap there is something to be said for the much criticized Higginson's syringe. If a catheter is slid over the bone nozzle there should be no risk of perforation, and the sharper rise in pressure it is possible to produce is most helpful. It is not always necessary: tube, funnel and water alone will often work, as evidenced by the number of returned rectal salines when given this way. If there is an objection to soap—and there is—there is an even greater one to turpentine for the same reason. Of other irritative substances, ox bile is perhaps the least offensive; it can be given in small bulk (10 oz. [285 ml.]), often a very useful point, and is effective and yet not too irritating. Enemas such as those of oil and gruel gain their effect by the pressure of an adequate quantity; they are very comfortable as they lubricate at the same time.

Fashions change in enemas as in most things, but if the principles of their administration are considered it is not difficult to apply them in their right context.

MARGARET LOUDEN, F.R.C.S.

NOTES AND QUERIES

Allergic Dermatitis of the Eyelids

QUERY.—A female patient, aged sixty years, has for the past twelve months been suffering from attacks of an allergic nature affecting the skin of the lids of her eyes, and the skin pouches below them. During an attack, which lasts for four or five days (once for a fortnight), the skin is red, puffy, swollen, and itches. The attacks occur about every three months and do not seem to have any relation to the usual allergic causes. She has never suffered in this way before. The first attack was a particularly severe one, closing up her eyes completely. Apart from this, she has a minor degree of rheumatic arthritis, affecting particularly her shoulders, mostly morning

pains, for which she takes aspirin. A young skin specialist has prescribed antistin tablets and calamine lotion for the eyes during attacks, and these seem to alleviate them slightly. Is there a name for this condition? I have heard of one other case. Do you think a $\frac{1}{4}$ -grain (16 mg.) thyroid tablet t.d.s. would help?

REPLY.—From the description of the case I should consider two possible diagnoses:—(a) A contact dermatitis caused by some external irritant to which the patient is periodically exposed. (b) A condition that I first described in 1934, and again in 1946, as follows:—

"The patient complains of recurrent attacks of 'swelling' of the lids, associated as a rule with intense itching. The attacks admittedly follow emotional disturbances, a sleep-

The rectal tube should be of good-sized bore (not less than $\frac{1}{2}$ inch) and should if possible be attached direct to a small funnel (3 to 4 ounce [85 to 115 ml.] capacity is convenient) containing about an ounce (28.5 ml.) of water. If any connexions are necessary in this part of the apparatus they must be of equal bore and not narrower. The funnel is arranged 1 to 1½ feet only above the level of the anus, is open to atmospheric pressure, and is replenished from a large reservoir suspended above, from which the fluid drips slowly through a drip chamber into the funnel. If the patient coughs and the intra-abdominal and therefore intra-rectal pressure is raised, the fluid in the funnel can be seen to rise markedly. Even respiratory movement can be seen in the funnel fluid level, which demonstrates that no increased pressure can be corked up in the bowel when this method is used, and experience shows that using it makes the absorption of up to 9 pints (5 litres) or even more in twenty-four hours a practicable matter.

INDICATIONS FOR USE

Evacuation of the bowel may have to be assisted or ensured: (1) when constipation is present; (2) when it is wished to make an endoscopic examination of the bowel; (3) when an operation on the bowel is intended; and (4) when obstruction is suspected and information sought as to whether the lower bowel is being filled from above. In the first three groups the employment of either enemas or aperients may be considered; in the fourth group it is essential to avoid aperients and employ only enemas.

Experience shows that it is still necessary to continue emphasizing the grave risk of perforation if an aperient is given in the presence of *obstruction*. An enema, on the other hand, is both safe and informative. If no result is obtained the diagnosis of obstruction becomes probable; if there is a result with the first enema the administration of a second, one or two hours later, with no result will have the same significance. It is just worth bearing in mind that something depends upon the person administering the enema. An inadequate enema may not empty completely the bowel below an obstruction and a second will therefore still produce a result, whilst an over-enthusiastic enema may cause such a clearance that a patient with no obstruction may produce nothing with a second attack. The importance of such fallacies is relative only to the difficulty of diagnosis, and should not, of course, be taken too seriously when all other evidence points in one direction.

Whether or not an enema is used for *constipation* depends in part upon the degree. In an acute, severe case, for example, a patient with a fissure-in-ano, whose rectum has become choked up with hard fæces on account of the pain of evacuation, the more comfortable method of assistance is by enema (occasionally digital evacuation under anaesthetic is required). Oil run in by catheter overnight to soften the fæces, followed by gentle repeated washouts to break away small pieces at a time, is the kindest treatment. In chronic constipation from atony, commonly seen in the aged, and in cases of adult megacolon, it may be essential to use enemas, at least occasionally.

PREOPERATIVE BOWEL EVACUATION

For many operations purgation is not necessary, and is indeed a harmful disturbance. Preoperative enemas are therefore not now employed so extensively as previously, although it should be noted that the practice dies much harder among the nursing than the medical profession. Inquiry reveals surprisingly often that the most trivial and irrelevant cases are prepared in this way. When it is necessary to have an empty bowel, of course the matter is different. Resections of the large bowel are safest when the bowel is both out of use and empty. A preliminary colostomy ensures the former and washouts the latter. Such washouts are best carried out through and through from colostomy to rectum, but before this can be achieved rectal washouts may be necessary. It is not often that a wash-through cannot eventually be obtained, as the final completion of an obstruction is usually by a fæcal plug in a narrowed lumen rather than complete obliteration of the lumen itself. Before such operations as hæmorrhoidectomy or sigmoidoscopy the choice between aperients and enemas

PRACTICAL NOTES

Oestrogens in the Treatment of Eczema of the Nipple

FROM their observations in 100 cases of eczema of the nipple and areola seen at the Kasr El-Ainy Hospital, Cairo, A. H. Shaaban and Hassan Seif El-Nasr (*British Journal of Dermatology and Syphilis*, June 1949, **61**, 216) consider that endocrine factors play a predominant rôle in those cases occurring: (a) in the early years of menstruation; (b) during pregnancy and lactation; (c) at and following the menopause. In their 20 cases in young girls, and 10 cases over the age of forty, rapid recovery followed the local application of an ointment containing 2 mg. of stilboestrol in 25 g. of lano-vaseline: complete cure resulted within a fortnight in 80 per cent. of the girls and in 60 per cent. of the menopausal women. In those cases which did not respond completely to local treatment, oestradiol benzoate (10,000 I.B.U.) was also given intramuscularly every fourth day. In cases occurring at other times during the menstrual life of the patient a stronger local application was required, and the following formula was found of value:—

Stilboestrol	250 mg.
Crude coal tar	5 g.
Zinc oxide	50 g.
Talc	50 g.
Liquid paraffin	20 g.
Vaseline	125 g.

When this ointment without the stilboestrol was used, there was little improvement in the condition. Cases occurring during pregnancy and lactation were found to be the most resistant to treatment.

Local Alcohol Injections in Hay Fever

THE results obtained by injection of alcohol into the nasal mucosa in over 100 patients with hay fever, of ages ranging from seven to fifty years, are recorded by Bedford Russell (*Lancet*, June 25, 1949, **1**, 1098). The method employed is as follows:—Using a solution of cocaine hydrochloride, 20 per cent., with equal parts adrenaline hydrochloride 1:1000, the nasal passage is lightly sprayed and the sensitive patches packed with ribbon gauze soaked with the same solution, for fifteen minutes. Starting at the postero-inferior border of the trigger area, a tiny drop of 70 per cent. alcohol is injected with a fine 3" needle; the next drop is introduced $\frac{1}{2}$ of an inch forward and upward, and so on until the mapped-out spot has been covered. Within an hour or two of injection the nasal passage is usually occluded by swelling of the mucosa and the formation of a plastic

exudate from the injected area. It is therefore inadvisable to inject both sides of the nose at the same time; four days later it is usually possible to free the injected nasal passage for breathing by removal of the exudate; the opposite side may then be treated. The patient is seen preferably a week or more before the expected sneezing is due to begin; if seen after the pollen season has begun it is less easy to anaesthetize the affected areas, and bleeding may occur. Of the cases treated, two patients treated in 1928 have been free from hay fever ever since. Both these patients were over forty years of age, and are stated to be exceptional. The usual result is to "reduce symptoms below the threshold of distress, and often to obliterate them for at least one season". Contraindications to the treatment are the presence of inflammation of the teeth or sinuses, and the rare "characteristic sensitivity over most of the nasal mucosa".

Nicotinic Acid and its Derivatives in Eye Infections

THE use of nicotinic acid in the forms of "niconic acid" (Wander) and "ronicol" (Roche), in combination with benerva and acetylcholine, in 19 cases of affections of the eye is recorded by H. E. Senn (*Praxis*, June 23, 1949, **38**, 569). The cases treated included: amblyopia due to excess of nicotine or alcohol (6); arteriosclerotic optical atrophy (5); optical atrophy from other causes (3); inflammatory optic nerve injuries (3); senile macular degeneration (2). The drugs were given in most cases by intravenous injection. Markedly good results were obtained in the cases of amblyopia due to nicotine or alcohol poisoning: in 2 patients visual acuity of 0.05 and 0.5 was increased to 1.0 and 1.25, and the improvement had been maintained eighteen months after treatment. In 3 other cases there was considerable improvement, and 1 case failed to respond. In the cases with arteriosclerotic optical atrophy, improvement of vision was obtained in only 2 of the 5 cases treated. Marked improvement was obtained in one case of optical atrophy due to non-vascular causes. In the remaining cases there was no response to treatment, except in 2 patients with inflammatory optic nerve injuries probably of tuberculous origin, in whom the treatment activated the process.

Papaverine in Epilepsy

ON the basis of the view that "cerebral vasoconstriction is causally related to the epileptic attack", H. I. Russek and B. L. Zohman (*New*

less night, or fatigue. There is œdema, which may be present alone, or may be accompanied by erythema, and sometimes by eczematization. As with eczematized seborrhœic dermatitis of the lids, the history and appearances may suggest a contact dermatitis, but there is one feature that is pathognomonic, namely the sharp limitation to the eyelids of the œdema, or, when present, of the erythema and eczematization. The sharp margination recalls that seen in one form of eczema of the nipples, in which the exact area of the areolæ is alone involved".

In my description of this condition of the eyelids, I wrote: "The patient is usually a highly strung woman, manifesting obvious signs of the anxiety state, and questioning will, as a rule, disclose either a long period of worry or stress, and acute infection from the effect of which she has not recovered, or more commonly some source of domestic unhappiness". Nearly all my patients have been women at the climacteric period, but I have seen one male case (*The Practitioner*, 1946, 156, 333).

If, as seems likely, the eruption in this case is not strictly confined to the eyelids, a contact dermatitis is more probable, and one is largely dependent upon the patient's intelligent co-operation in the search for the responsible irritant. Hair lotions or dyes may cause a dermatitis of the eyelids without affecting the scalp and neighbouring parts, and the same is true of other irritants, since the skin of the eyelids is extremely sensitive. Presumably the aspirin referred to is taken frequently and can be excluded as the cause.

H. W. BARBER, M.B., F.R.C.P.

The Stimulant Action of Dexedrine

QUERY.—I have lately been very impressed with the "tonic" effect of 1 dexedrine tablet, or in some cases even $\frac{1}{2}$ a tablet, given at breakfast time, in certain patients complaining of general lassitude and lack of energy, patients in whom there are no signs of physical disease to account for lack of energy, such as tuberculosis or anæmia. These patients tell me that they never felt better in their lives, have much more energy, and feel that life is altogether different for them. I should be very grateful for information on the following points: (1) Whether any harm can result from continuing this dosage indefinitely; (2) whether the drug is habit forming, and whether the dosage would consequently have to be increased to maintain the effect; (3) whether there are likely to be any unpleasant withdrawal symptoms. Incidentally, I have not noticed any reduction in weight or loss of appetite on this dosage, and the patients most benefited are those with low systolic blood pressure, e.g. 95 to 100, but no signs suggestive of Addison's disease.

REPLY.—Dexedrine is a proprietary name for dextro-amphetamine sulphate, a member of the sympathomimetic group of drugs, which have to a greater or less extent a stimulant action on the higher centres of the brain similar to the action of caffeine. In this respect amphetamine is the most powerful member of the group and patients suffering from exhaustion or a "hang-over" from alcohol often derive considerable

subjective benefit from the drug. Improved cerebration, a lifting of depression and a feeling of well-being are quite common after a dose of 5 or 10 mg. One dexedrine tablet contains 5 mg. of the drug and no harm can result from continuing this small dose indefinitely. Indeed no organic change has been noted even after the prolonged administration of large doses, although tachycardia, sleeplessness, psychological disorders and loss of weight may result. Some habituation to the drug undoubtedly occurs and amphetamine addicts have been encountered, but there is no reason to fear this fell result from the administration of 5 mg. a day, although in the course of time it might cease to have much effect; nor need the occurrence of withdrawal symptoms be anticipated even if two to three times that dose were employed.

PROFESSOR D. M. DUNLOP, M.D., F.R.C.P., F.R.S.E.

Treatment of Ulceration of the Mouth in Children

QUERY.—I shall be grateful if you can let me have some information on the most up-to-date treatment of ulceration of the mouth in children.

REPLY.—Herpetic stomatitis is much the most common cause of ulceration of the mouth in children. It is caused by the herpes simplex virus. The vesicles usually ulcerate and secondary infection occurs with mixed organisms, such as streptococci and staphylococci. Thus a more general stomatitis and gingivitis is produced. *Monilia albicans* (thrush) is a common secondary invader, and Vincent's organisms occasionally assert themselves, particularly in debilitated patients. This type of stomatitis, which is commoner in the early years of life, is often associated with severe malaise and high fever for a few days. The oral discomfort prohibits the ingestion of food and curtails the intake of fluid to a minimum.

Treatment consists in the frequent administration of sips of bland fluid, such as milk and sugar, and very dilute fruit drinks with sugar. Acid fruit drinks may irritate the ulcerated areas. Some semi-solid food can be tolerated after a few days. Older children may be induced to wash the mouth out frequently with an antiseptic mouth wash, such as glycerin of thymol. Young children should have gentian violet, 1 per cent. in aqueous solution, applied to the mouth twice a day, or glycerin of borax several times a day. It is seldom necessary to cleanse the ulcers with swabs dipped in hydrogen peroxide. Sulphonamide should be given systemically to combat secondary invaders, also penicillin in severe cases.

J. L. HENDERSON, M.D., F.R.C.P. ED.

PRACTICAL NOTES

Oestrogens in the Treatment of Eczema of the Nipple

FROM their observations in 100 cases of eczema of the nipple and areola seen at the Kasr El-Ainy Hospital, Cairo, A. H. Shaaban and Hassan Seif El-Nasr (*British Journal of Dermatology and Syphilis*, June 1949, **61**, 216) consider that endocrine factors play a predominant rôle in those cases occurring: (a) in the early years of menstruation; (b) during pregnancy and lactation; (c) at and following the menopause. In their 20 cases in young girls, and 10 cases over the age of forty, rapid recovery followed the local application of an ointment containing 2 mg. of stilbœstrol in 25 g. of lano-vaseline: complete cure resulted within a fortnight in 80 per cent. of the girls and in 60 per cent. of the menopausal women. In those cases which did not respond completely to local treatment, œstradiol benzoate (10,000 I.B.U.) was also given intramuscularly every fourth day. In cases occurring at other times during the menstrual life of the patient a stronger local application was required, and the following formula was found of value:—

Stilbœstrol	250 mg.
Crude coal tar	5 g.
Zinc oxide	50 g.
Talc	50 g.
Liquid paraffin	20 g.
Vaseline	125 g.

When this ointment without the stilbœstrol was used, there was little improvement in the condition. Cases occurring during pregnancy and lactation were found to be the most resistant to treatment.

Local Alcohol Injections in Hay Fever

THE results obtained by injection of alcohol into the nasal mucosa in over 100 patients with hay fever, of ages ranging from seven to fifty years, are recorded by Bedford Russell (*Lancet*, June 25, 1949, **i**, 1098). The method employed is as follows:—Using a solution of cocaine hydrochloride, 20 per cent., with equal parts adrenaline hydrochloride 1:1000, the nasal passage is lightly sprayed and the sensitive patches packed with ribbon gauze soaked with the same solution, for fifteen minutes. Starting at the postero-inferior border of the trigger area, a tiny drop of 70 per cent. alcohol is injected with a fine 3" needle; the next drop is introduced $\frac{1}{4}$ of an inch forward and upward, and so on until the mapped-out spot has been covered. Within an hour or two of injection the nasal passage is usually occluded by swelling of the mucosa and the formation of a plastic

exudate from the injected area. It is therefore inadvisable to inject both sides of the nose at the same time; four days later it is usually possible to free the injected nasal passage for breathing by removal of the exudate; the opposite side may then be treated. The patient is seen preferably a week or more before the expected sneezing is due to begin; if seen after the pollen season has begun it is less easy to anaesthetize the affected areas, and bleeding may occur. Of the cases treated, two patients treated in 1928 have been free from hay fever ever since. Both these patients were over forty years of age, and are stated to be exceptional. The usual result is to "reduce symptoms below the threshold of distress, and often to obliterate them for at least one season". Contraindications to the treatment are the presence of inflammation of the teeth or sinuses, and the rare "characteristic sensitivity over most of the nasal mucosa".

Nicotinic Acid and its Derivatives in Eye Infections

THE use of nicotinic acid in the forms of "niconic acid" (Wander) and "ronicol" (Roche), in combination with benerva and acetylcholine, in 19 cases of affections of the eye is recorded by H. E. Senn (*Praxis*, June 23, 1949, **38**, 569). The cases treated included: amblyopia due to excess of nicotine or alcohol (6); arteriosclerotic optical atrophy (5); optical atrophy from other causes (3); inflammatory optic nerve injuries (3); senile macular degeneration (2). The drugs were given in most cases by intravenous injection. Markedly good results were obtained in the cases of amblyopia due to nicotine or alcohol poisoning: in 2 patients visual acuity of 0.05 and 0.5 was increased to 1.0 and 1.25, and the improvement had been maintained eighteen months after treatment. In 3 other cases there was considerable improvement, and 1 case failed to respond. In the cases with arteriosclerotic optical atrophy, improvement of vision was obtained in only 2 of the 5 cases treated. Marked improvement was obtained in one case of optical atrophy due to non-vascular causes. In the remaining cases there was no response to treatment, except in 2 patients with inflammatory optic nerve injuries probably of tuberculous origin, in whom the treatment activated the process.

Papaverine in Epilepsy

ON the basis of the view that "cerebral vasoconstriction is causally related to the epileptic attack", H. I. Russek and B. L. Zohman (*Nerv*

York State Journal of Medicine, June 1, 1949, 49, 1315) have used papaverine hydrochloride as a prophylactic for the control of grand mal seizures in two cases of confirmed epilepsy. The drug was given orally: in one case, that of a six year old boy, in dosage of 2 g. four times daily, and in the other case, a thirty-two year old male, in dosage of $4\frac{1}{2}$ grains (0.3 g.) four times daily. Both patients had previously been treated with dilantin and phenobarbitone without much improvement. In both cases there was cessation of epileptic seizures following the institution of papaverine therapy; in the first case over a period of six months, and in the second over a period of eight months. In the first case the child had the usual aura without the subsequent epileptic seizure. In the second case the substitution of placebo medication for one week resulted in two attacks. It is stated in conclusion that "further studies are indicated to evaluate this therapy for epilepsy and for the vasoconstrictor phase of migraine. Dosage as high as 15 to 18 grains (1 to 1.2 g.) per day may be essential to a satisfactory response".

Vaginal Instillation of Sulphathiazole after Delivery

THE instillation of sulphathiazole powder into the vagina immediately after delivery has been carried out in a large series of cases at the Glenville Hospital and Booth Memorial Hospital, Cleveland, Ohio. The method adopted and results obtained are described by C. W. Rotter and R. H. Long (*American Journal of Obstetrics and Gynecology*, May 1949, 57, 925). The method was as follows:—After the baby and placenta had been delivered and all necessary repair completed and bleeding controlled, the labia were separated with two fingers and 5 g. of sulphathiazole powder instilled deep into the vaginal tract and spread down into the posterior fornix and about the cervix with the index and middle fingers. In cases so treated it was noted that the amount of lochia was suppressed and also the offensive odour. Among the patients so treated redness and oedema of episiotomy wounds occurred in 19.3 per cent. compared with 40.5 per cent. in those not treated by instillation of sulphathiazole powder. Other points noted were: (1) No occurrence of wound disruption among the sulphathiazole-treated cases; four instances among those not so treated. (2) A tendency to lower temperature elevation among the treated cases. (3) Pain, especially in episiotomy cases, required medication in 32.2 per cent. of the treated cases compared with 55.2 per cent. in the untreated. No untoward reactions were noted.

Glycocoll in the Treatment of Angina Pectoris

THE use of glycocoll in the treatment of 52 cases of angina pectoris is recorded by M. Audier and G. Dumon (*Presse Médicale*, June 18, 1949, 57, 570). All the cases treated had the clinical symptoms and electrocardiographic signs of true angina pectoris. A 10 per cent. glycocoll solution was employed, 10 ml. being injected intravenously each day, for ten days. The good results are observed after the fourth or fifth injection, in the form of amelioration of pain and a feeling of well-being and regained strength. If there is no modification of symptoms after ten injections it is useless to proceed with the treatment. On the other hand, if the crises are fewer or have ceased it is important to continue the treatment after five or six days' interval, as follows:—Five intravenous injections followed by an interval of ten days, and continued thus for three to six months; then a series of ten injections each month for three to six months. The actual regime varies with each patient and the results obtained. Of the patients treated, 25 received great benefit; in 15 the treatment failed or the benefit was slight or of short duration; in 12 cases maintenance therapy was necessary.

Clubbing of the Fingers

CLUBBING of the fingers may be classified into three groups: (1) symmetrical, involving all the fingers and toes; (2) unilateral, involving the fingers or toes of one hand or foot; (3) unidigital involving only one finger. In an article dealing with the pathology, clinical features and diagnostic significance of clubbing of the fingers A. Whitley Branwood (*Edinburgh Medical Journal*, March 1949, 56, 105) stresses the following points:—(1) Symmetrical, or bilateral clubbing may be acquired or hereditary. In the former case the condition may indicate a cardiac affection; some septic process in the lung or bronchial carcinoma; chronic bacillary or amoebic dysentery, ulcerative colitis, sprue or biliary cirrhosis. The digital clubbing in such cases can indicate the progress or disappearance of the disease, e.g., it may disappear following drainage of an empyema, or the treatment of subacute bacterial endocarditis with penicillin but if it still persists, failure to eradicate the disease or some underlying lesion must be suspected. The hereditary type may occur without any preceding or accompanying disease, or may indicate congenital heart disease. (2) Unilateral clubbing should suggest some condition affecting the vessels or nerves of the arm or at the thoracic outlet, e.g. aneurysm, carcinoma of the apex of the lung, costo-clavicular syndrome.

(3) Unidigital clubbing is rare, but cases have been recorded following an injury to the arm with damage to the median nerve, in Boeck's sarcoidosis, gout, and following injury to the finger. In differential diagnosis, acromegaly, osteoarthritis, rheumatoid arthritis, Heberden's nodes, syphilitic or tuberculous dactylitis and brachydactyly must be borne in mind.

Skin Protection with Antihistamine Ointments in X-Ray Therapy

THE successful use of the antihistamine drugs, both orally and locally, for skin protection in patients undergoing X-ray therapy, is recorded by M. P. Mains (*Radiology*, April 1949, 52, 579). For the ointments, benadryl or pyribenzamine, 5 per cent. in "aquaphor" base, was employed, the ointment being applied to all irradiated areas immediately after treatment, and again at bedtime. In addition, the patients were given benadryl or pyribenzamine orally, 25 mg. before each meal. It is recorded that even with doses as high as 2,400r in air, local reactions were much less than those formerly observed with doses of 1,800r in air, also subjective reactions in the form of bowel and bladder symptoms appeared to be less. As an example, one of the recorded cases may be quoted:—

The patient was receiving treatment for carcinoma of the floor of the mouth with cervical metastases, a portal about 15 cm. square being used on each side of the neck and face, with a dosage to each of 2,400r in air. Two additional small portals under the chin and over the mouth were also used. The patient was given benadryl, 25 mg. orally before each meal, and the ointment was applied after treatment and at bedtime. He continued to shave during the course of irradiation, and at no time suffered more than a mild erythema. Examination five months after completion of the course of treatment showed an apparently normal skin, with no appreciable atrophic changes, and return of beard growth over most of the areas.

Similar good results are claimed in over 100 cases treated: "Objectively the patients showed a markedly increased skin tolerance to radiation. We believe tolerance has been enhanced by the local use of an anti-histamine drug, although oral administration may have some influence. . . Animal experiments are contemplated to give proof of the protective value of these drugs to the irradiated skin, and of their value in combating the histamine produced by irradiation".

Care of the Skin in the Newborn

A SIMPLE method for care of the skin of the newborn has been in operation at the Unity Hospital, Brooklyn, New York, since 1927, during which time over 23,000 new-born babies have been admitted and discharged from the maternity service without, apart from one case in which the method was disregarded, any

outbreak of skin infections among the babies. The method, which is described by H. Apfel (*Archives of Pediatrics*, March 1949, 66, 131), is based on the view "that the vernix caseosa is a necessary protective covering which serves as a lubricant to the baby's skin". Thus it should be preserved. After serving its purpose it dissolves by normal body temperature "without any interference", and the baby's skin is found to be soft, clean and pink. The method is also stated to "spare the break in the superficial layers of the skin which is unavoidable when massaging or anointing with oil". The technique adopted is as follows:—"The baby is wrapped in soft warm blankets. The eyes are given the usual prophylactic treatment; the cord is securely tied and wrapped in sterile gauze saturated in 70 per cent. alcohol and secured with a narrow band". Soon after this the baby is dressed in shirt and diaper, which are changed as often as necessary and any mucus, blood or other discharge wiped away with clean cotton-wool moistened with warm water. The infant is not given a bath until the cord has come away, which is some time after leaving the hospital. The mother is shown how to continue the technique used at the hospital nursery, and is instructed not to apply or massage any oil on the baby's skin at any time.

Treatment of Hypertension

A NOTE on the results obtained by Grimwald (*Sovietskaja Meditsina*, 1948, 5) by the use of the Steinberg-Barschak method of treatment of hypertension appears in *Médecine et Hygiène*, March 15, 1949, 17, 84. The method consists in the alternative administration daily of 10 ml. of 20 per cent. solution of sodium hyposulphite and 10 ml. of a 40 per cent. glucose solution, to which is added 2 ml. of a 25 per cent. solution of magnesium sulphate, by intravenous injection. The treatment is not begun until the seventh to fourteenth day of hospitalization, when it is determined that there is no important fluctuation of the blood pressure. A course of eight to twenty injections is given. No success was obtained in cases of malignant hypertension, but in the other forms the blood pressure became normal in 10 cases, was improved in 28, and remained stationary in 7 of the 50 cases treated. It was noted that the systolic pressure could be reduced more easily than the diastolic. The cerebral symptoms were markedly relieved: five to seven days after the beginning of treatment there was disappearance of headache and vertigo. Also, in 17 cases there was diminution of the cardiac symptoms. A follow-up in 34 cases showed that the good results were maintained eight months after cessation of treatment.

REVIEWS OF BOOKS

Handbook of Midwifery. By MARGARET PUXON, M.D., M.R.C.O.G. London: Sylviro Publications Ltd., 1949. Pp. 326. Price 25s.

THE preface states that this book is written primarily for examination candidates and general practitioners. The needs of these groups differ sufficiently to make it difficult to satisfy both, and the impression conveyed in this case is that the author has had the examination candidate chiefly in mind. The general practitioner in domiciliary practice would, for instance, have difficulty in carrying out the instruction on p. 71, to change his gown and gloves if he has to attend to the child before completing treatment of the mother after labour. In addition, the general practitioner faced with a case of obstructed labour would have found helpful a section on, and index reference to, this subject. The examination candidate will be particularly attracted to this book as it is a mine of information clearly and concisely set out. In many places the unavoidable condensation gives an appearance of dogmatism concerning matters on which not all obstetricians would agree. Fœtal asphyxia is treated rather summarily and the chief reference to it in the text (p. 70) is not mentioned in the index. On p. 78, progesterone is recommended in cases of threatened abortion but there is no mention of the Guterman test. The description of the management of normal labour is good, but surely the footnote to p. 70 should read "... the head should not be allowed to extend ..."? The chapters on breech delivery, contracted pelvis and the Rhesus factor are particularly well done and the book as a whole creates a good impression. It is set in legible type, with few printers' errors, and is well produced, although devoid of illustrations. It can be recommended particularly to examination candidates and to general practitioners who require easily accessible information on specific points in obstetrics for rapid reference.

Maternity in Great Britain. (A survey of Social and Economic Aspects of Pregnancy and Childbirth undertaken by the Joint Committee of the Royal College of Obstetricians and Gynaecologists and the Population Investigation Committee.) London: Oxford University Press, 1948. Pp. xvi and 262. Price 12s. 6d.

THIS interesting book has been produced as the result of interviewing nearly 14,000 women who were delivered in one week in 1947. The object of the inquiry was to study the social

and economic aspects of pregnancy, to assess the value of the maternity services to the community, and to ascertain the average cost incurred by parents in the first and succeeding pregnancies. The book will be found most useful to those concerned with maternity work, as indicating both the value of the services as at present in being, and also the lines on which further improvement will make their efforts even more valuable.

Obstetric Analgesia and Anaesthesia. By FRANKLIN F. SNYDER, M.D. Philadelphia and London: W. B. Saunders Company, 1949. Pp. viii and 401. Figures 114. Price 32s. 6d.

By an ingenious experimental method devised by himself and Rosenfeld, Dr. Snyder has been able to investigate in the rabbit some of the problems arising from the discovery that the fœtus breathes *in utero*. The respiratory troubles of the fœtus and the newborn, such as asphyxia, pneumonia and atelectasis, are studied in the light of this knowledge; their consideration makes fascinating reading, and occupies the first section of the book. In the second section the same method is used to investigate the merits and demerits of the various analgesics used in labour, and the experimental findings are correlated with clinical reports, each drug being appraised in turn. In view of present trends in obstetric analgesia over here, it is unfortunate that Minnitt's work and his apparatus are not mentioned, that there is only a brief and non-committal account of pethidine (demerol), and that trichlorethylene does not appear at all. It is also surprising that there is no reference in the text to the work of Barcroft after 1938. In spite of these omissions the book is a notable contribution to the literature.

Anaesthesia for the Poor Risk. By WILLIAM W. MUSHIN, M.B., B.S., F.F.A., R.C.S., D.A. Oxford: Blackwell Scientific Publications, 1948. Pp. ix and 65. Price 7s. 6d.

ANÆSTHESIA for the poor risk is the subject of the first of twenty-eight short essays in this sixty-five page volume. The title on the outer cover is therefore somewhat misleading, as four pages only are devoted to the poor risk patient. These essays discuss, in a leisurely style, many everyday problems of anaesthesia, some controversial aspects, such as the position of ether in modern anaesthesia, and some rare ones, such as anaesthesia by hypnosis. The range of subjects is wide. Most anaesthetists will agree with these

reflections of an experienced anæsthetist. Although details and methods of anæsthesia are not taught here, general practitioners, physicians, and especially surgeons, will find this book useful, for it expresses balanced modern ideas on anæsthesia, and it can easily be read in an evening. The production and layout are attractive.

Physician Extraordinary. BY SHIRLEY MURRELL. London: Hodder & Stoughton Ltd., 1949. Pp. 318. Price 10s. 6d.

THIS pleasantly written novel based upon the life of Sir Gilbert Blane will appeal to many medical readers. Naturally, pride of place is given to Blane's great work in introducing lime juice as a cure and preventive for scurvy in the Royal Navy, and full advantage is taken of his association with the Prince Regent for the purpose of lending a colourful background to the story. His association with Jenner in popularizing vaccination against smallpox is not woven into the plot with quite so much skill. By many of the younger generation this may well be regarded as a somewhat insipid novel, as acts of violence, immorality and sadism are conspicuous by their absence. Neither is there any attempt to pander to the craving of Bloomsbury for psycho-analysis. On the other hand, for those who, like the reviewer, prefer an old-fashioned tale, retailed with respect for the King's English, this is a novel which can safely be recommended. It would make ideal holiday reading.

A History of Oto-Laryngology. BY R. SCOTT STEVENSON, M.D., F.R.C.S.ER., and DOUGLAS GUTHRIE, M.D., F.R.C.S.EO. Edinburgh: E. & S. Livingstone Ltd., 1949. Pp. vii and 155. Figures 52. Price 17s. 6d.

THIS small, well-illustrated book can be strongly recommended. The reviewer first read it through from cover to cover during a long and tedious train journey, to find his interest never flagged despite the inclusion of just as many dates and names as those found in schoolboy history books. These dates and names are essential in a book which will be useful to those writing the introductory passages to papers on ear, nose and throat subjects. Readers who become confused by dates and names need not worry, because the story of human endeavour is unfolded in such a fascinating manner. Perhaps the most startling fact that emerges is that the early pioneers were able to do much, years before adequate examination instruments were designed. Full honour is paid to the "moderns" of the 20th century whose strides aided by

up-to-date equipment have speeded up progress, but the authors have rightly stressed our even greater debt to earlier "giants" such as Duverney, who published a monograph on the subject of otology in 1683. Erroneous preconceived ideas are quietly corrected. Schwartze, whose name is still honoured as the originator of the cortical mastoid operation, was in reality the man who, with Eysell and Kuster, showed that the operation was a practical measure. We learn that both Petit and Jasser had successfully opened the mastoid process a hundred years before. It is to be hoped that the authors may in the future find time to write a book of greater length so that we may know even more of the personalities of those fascinating characters described all too briefly. An excellent balance has been struck between the British and foreign contributions to otolaryngology, although perhaps the picture of American progress is somewhat too condensed.

NEW EDITIONS

DELETION of out-of-date material and the addition of recent advances have been carried out in the preparation of *Textbook of Midwifery*, by Wilfred Shaw, M.D., F.R.C.S., F.R.C.O.G., in its third edition (J. & A. Churchill Ltd., 22s. 6d.). Since the appearance of the previous edition in 1947, penicillin has become firmly established in the treatment of gonorrhœa, syphilis and puerperal sepsis, and sections on its use have been included. The new edition is well illustrated.

A Short Practice of Surgery, by Hamilton Bailey, F.R.C.S., F.A.C.S., F.I.C.S., F.R.S.E., and R. J. McNeill Love, M.S., F.R.C.S., F.A.C.S., F.I.C.S., in its eighth edition, in five parts (H. K. Lewis & Co., Ltd., 52s. 6d. the set) contains a new chapter on peptic ulcer. The new edition is well produced and richly illustrated, many of the figures being in colour.

CONSIDERABLE rewriting has been undertaken in the preparation of the twelfth edition of *Clinical Methods*, by Sir Robert Hutchison, Bt., M.D., F.R.C.P., and Donald Hunter, M.D., F.R.C.P. (Cassell and Company Ltd., 17s. 6d.) and a number of new sections have been added, dealing respectively with liver function tests, fat in the fæces, and X-ray examination of the intestinal tract and the chest. Some new plates have been included.

The Rhesus Factor, by G. Fulton Roberts, M.A., M.B., in its second edition (Wm. Heinemann [Medical Books] Ltd., 3s. 6d.) is a concise and clear exposition of this important and complicated subject. There is a useful chapter on treatment.

NOTES AND PREPARATIONS

NEW PREPARATIONS

FEL-EVAC, a standardized fatty meal for cholecystography containing 40 per cent. edible vegetable oils and animal fats, is supplied in packages of six tubes, each tube containing $1\frac{1}{2}$ ounces, sufficient for one dose. (Allen & Hanburys Ltd., Bethnal Green, London, E.2.)

FLAXEDIL, tri-(β -diethylaminoethoxy)-benzene triethiodide, is a synthetic curarizing compound which is stated to be as effective as *d*-tubocurarine and to possess certain advantages. Its use is indicated to procure muscular relaxation under light anaesthesia, to minimize the convulsions of shock therapy, and in some spastic conditions. It is supplied as a 4 per cent. solution in ampoules of 2 ml. (80 mg. of the active drug), in boxes of 10. (May & Baker Ltd., Dagenham, Essex.)

MYCIL. PESSARIES contain 4 per cent. of the fungicidal substance, *p*-chlorophenyl- α -glycerol ether, in a water-soluble base. Their use is indicated in the treatment of vulvo-vaginal mycosis and vaginal thrush. They are issued in tubes of 12. (British Drug Houses Ltd., Graham Street, London, N.1.)

Digophyllin A.F.D. (digitoxin and aminophylline) will in future be known as **DI-CARDINE**. (Anglo-French Drug Co. Ltd., 11 & 12 Guilford Street, London, W.C.1.)

THE CIBA FOUNDATION

ON June 22, 1949, Sir Henry Dale, O.M., F.R.S., President of the Royal Society of Medicine, opened the Ciba Foundation at 41 Portland Place, London, W.1. The premises have been acquired by Ciba Ltd., who are also providing the funds for the Foundation, for the purpose of establishing a scientific centre where scientists from all countries may stay with the object of meeting and exchanging ideas. The funds of the Foundation are vested in trustees—Lord Beveridge, Lord Horder, Prof. E. D. Adrian, O.M., F.R.S., and Mr. Raymond Needham, K.C.—who have sole control of the policy of administration. The Secretary is Dr. G. E. W. Wolstenholme.

THE ROYAL SOCIETY OF MEDICINE at the Annual Meeting of the Royal Society of Medicine on July 5, 1949, the following received their Diplomas as Honorary Fellows:—

Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.
Dr. Brock Chisholm, Director, General World Health Organization.
Sir Gordon Gordon-Taylor, K.B.E., C.B., M.S., F.R.C.S., F.A.C.S.
Dr. Alan Gregg, of the Rockefeller Foundation.
Professor René Lenche (Paris).

THE MEDICAL DIRECTORY

J. A. CHURCHILL LTD., publishers of *The Medical Directory*, write:—"To maintain the

accuracy of our annual volume we rely upon the return of our schedule, which has been posted to each member of the medical profession. Should the schedule have been lost or mislaid we will gladly forward a duplicate upon request. The full names of the doctor should be sent for identification".

OFFICIAL NOTICE

B.C.G. Vaccination.—Arrangements have been made by the Ministry of Health to introduce B.C.G. vaccination against tuberculosis in this country. As the method has yet to be put to the test of experience under conditions native to this country it has been decided that the scheme should be kept within controlled limits and to start with, B.C.G. vaccination will be offered to all hospital nursing staffs and medical students, and secondly, will be made available to all chest physicians or other appropriate specialists, e.g. paediatricians, who may wish to use the vaccine in suitable cases on their individual responsibility.

PUBLICATIONS

Foot Inspection in Childhood and Adolescence published by the Foot Health Education Bureau, 121 Ebury Street, London, S.W. price 1s., or 15s. per 100 copies, has been issued "in the hope that it may be of service to Medical Officers at routine medical inspections". A Conference on "Foot Inspection in Childhood and Adolescence", at which Mr. T. T. Stamp, F.R.C.S., will demonstrate methods of examining the feet, will be held at Caxton Hall, London, on September 30, 1949.

The Mental and Physical Effects of Pain, by V. C. Medvei, M.D., M.R.C.P. (E. & J. Livingstone Ltd., price 3s.) is a reprint of the Buckston Browne Prize Essay, Harveian Society of London, 1948.

"*Paramisal*" (para-aminosalicylic acid) and "*Paramisal Sodium*" (sodium para-aminosalicylate) deals with the pharmacology and therapeutic uses of these products. A copy of the brochure is available on application to Herts Pharmaceuticals Ltd., Bessemer Road, Welwyn Garden City.

Vademecum of Therapeutics and Products, giving details of the properties and administration of Sharp and Dohme Ltd.'s products, and including a section on general information useful to medical practitioners, is available on application to West Hill Laboratories, Hoddesdon, Herts.

The contents of the September issue, which will contain a symposium on "Diseases of the Eye", will be found on page lxvi at the end of the advertisement section.

THE PRACTITIONER

No. 975

SEPTEMBER 1949

Volume 163

THE EYE IN GENERAL MEDICINE

By A. J. BALLANTYNE, M.D., LL.D., F.R.F.P.S.

Emeritus Professor of Ophthalmology, University of Glasgow.

It would be impossible in the space of a single article to give more than a sketchy outline of the relations of the eye to general medicine. I propose therefore to draw attention to one or two selected groups of cases which have some points of interest common to the general practitioner and the ophthalmic surgeon.

There are, of course, several lines of approach to every problem in "systemic ophthalmology". The physician may be consulted with regard to symptoms for which he thinks the eyes will provide an explanation: headache is a typical example; or in a case already diagnosed he may seek the help of the oculist in regard to prognosis: the ocular complications of pregnancy are a case in point. Occasionally a patient whose condition is puzzling is submitted to the oculist, as to the rhinologist, the neurologist, the radiologist and others, in order that no stone may be left unturned and no sign or symptom overlooked; and quite often, in the course of a refraction test, the oculist discovers some pathological condition of the fundus calling for medical investigation and treatment.

In what follows I shall deal with some of the problems thus suggested, under the headings of symptomatology, etiology, diagnosis and prognosis.

SYMPTOMATOLOGY

Sudden or rapid failure of vision.—This is a leading symptom which often presents itself to the physician. It may be the sole complaint; there is no symptom which covers a larger field of possible causes, and none in which the patient's story may be more misleading or, at least, unhelpful.

A history of sudden loss of vision should not be accepted without a certain amount of caution, for it is remarkably easy for the patient to be deceived as to the suddenness of the onset. The sudden discovery of a pre-existing defect is not uncommonly mistaken for its sudden occurrence. Such a mistake, of course, is only possible because the patient has two eyes and is only made aware of the monocular defect when some trifling incident causes him to close the better eye.

Among the most common, and most serious, causes of sudden loss of sight may be mentioned the homonymous hemianopia due to a lesion of the visual cortex or optic radiations; detachment of the retina; intra-ocular hæmorrhage; and obstruction of the central vein or central artery of the retina.

In *detachment of the retina*, at whatever point the detachment may occur, the sub-retinal fluid tends to settle in the lower part of the eye, with the result that the visual defect is noted in the upper half of the field like a dark curtain or shadow. Even before the ophthalmoscopic examination is made the cause of the trouble may be suggested by a simple confrontation test of the field of vision. Finger movements make a good test object for this purpose, and a similar test will serve to map out a *homonymous hemianopia*, so as to convince the patient that what was believed to be blindness of one eye is in reality a binocular half-field defect.

A sudden darkening of the whole field of vision is more probably due to *hæmorrhage into the vitreous*. Such a hæmorrhage may be so slight as to cast a reddish shade over the whole field, or so severe as to abolish light perception. A special form of *recurrent intra-ocular hæmorrhage* is found in "Eales's disease", which affects both men and women in the second and third decades. There may be many minor attacks of hæmorrhage into the vitreous, with intervals of apparently complete recovery, before secondary changes, such as the organization of blood clots and detachment of the retina, set in, leading in many cases to loss of the eye. There is reason to believe that, in some cases at any rate, the vascular disease which permits the occurrence of the hæmorrhage is of tuberculous origin.

The immediate effect of *obstruction of the central retinal artery or vein* is a practically total blindness of the eye. These two disorders are easily distinguished in ophthalmoscopic examination. Obstruction of the artery, usually referred to as "embolism of the central artery", if complete, causes an ischæmia of the whole retina and, since the viability of the retina deprived of its blood supply is only a matter of minutes, the ultimate result is usually blindness of the eye, with perhaps a small area of light perception in the temporal half of the peripheral field. Sometimes a happier outcome is experienced, for if the obstruction is due to arterial spasm the ischæmia may be short-lived, whilst if it is the result of a true embolism, the embolus may break up or move on to a smaller branch and thus allow a degree of recovery. The immediate cause of the visual loss in venous obstruction is the occurrence of multiple, and often large, hæmorrhages throughout the retina. This, and the resulting œdema, may be so severe that the retinal arteries are completely eclipsed, and only short, distended and tortuous segments of the veins may be visible. The prognosis as regards vision is usually bad, even when the hæmorrhages are absorbed in the long run, but sometimes a useful amount of vision is restored.

Another example of sudden or rapid loss of vision is that due to *retro-*

bulbar optic neuritis. The retrobulbar site of the lesion in this case accounts for the fact that it rarely leads to any immediate change in the optic disc; but there are sometimes features in its onset that make the diagnosis clear. The lesion in the nerve affects the axial bundles and thus causes a central scotoma in the field of vision; movements of the eyes are painful, and a deep-seated tenderness is felt if the eye is pressed backwards in the orbit. This describes the acute form, but a retrobulbar neuritis may occur in a quiet form. In this case also, the onset appears to be sudden. An important and characteristic feature is the tendency to complete visual recovery, and the not uncommon history of an earlier or subsequent attack of transient diplopia completes a picture which is strongly suggestive of disseminated sclerosis.

Binocular visual affections.—The examples of sudden or rapid loss of vision which we have already discussed may be classified as monocular, but the second eye is not to be considered immune, and in all of them the disease may ultimately be binocular. The most typically binocular affections are those due to toxic influences, such as the toxæmias of pregnancy, or to quinine and other potent drugs.

The occurrence of binocular amblyopia or amaurosis in the course of pregnancy is usually a sign of the pre-eclamptic state, and calls for close attention, for its occurrence indicates an unfavourable prognosis for the vision and even for the life of the patient, and termination of the pregnancy may be called for.

Less common, but of equal concern in regard to the vision and life of the patient, is the loss of vision sometimes resulting from *hyperemesis gravidarum*. There is reason to believe that the cause, or an important part of the cause, is the loss of the food vitamins resulting from the perpetual vomiting; but toxins of unknown identity probably play a part. Here also the loss of vision may be complete; but whereas in the pre-eclamptic form there is little to be seen but a general narrowing of the retinal arteries, hyperemesis may produce retinal hæmorrhage and papillœdema. The visual loss in hyperemesis gravidarum is almost certainly due to retrobulbar neuritis, which manifests itself in a central scotoma, and the discovery of this defect at an early stage may be a valuable warning sign. Both in early and in advanced stages good results have followed the intensive administration of vitamins B₁ and C.

Quinine blindness has some unique features, and deserves special mention. Although the drug has been used extensively, over long periods and in large doses, the number of cases is small in this country, not more than two or three cases in the lifetime of one ophthalmologist. It has often happened that the dose which brought on the symptoms was quite moderate in amount, and idiosyncrasy evidently plays an important rôle. The onset of the blindness may be sudden, and the defect may amount to complete loss of light perception. Other signs may be wide inactive pupils, deafness, and

disturbance or even loss of consciousness. If the fundi are examined within an hour or two the only abnormality may be a fullness of all the retinal vessels; but soon the vessels, especially the arteries, show a progressive narrowing of calibre, accompanied by pallor of the disc—a general ischæmia of the retina. When improvement begins it is soon observed that the central part of the retina is the first to recover, the peripheral field improving more slowly and often incompletely. However great the improvement, the ischæmic picture in the fundus is permanent.

In cases of temporary amblyopia due to *vascular spasm* the field of vision is the best guide to the site of the obstruction. If the arteries of the retina and optic nerve are involved, the amblyopia will affect one eye at a time, and if there is an anomaly of the field it will be in the form of a sharply defined sector. To this should be added the fact that the retinal arteries may show some degree of sclerotic change. In the case of a cerebral vascular spasm, as in migraine, the field will be disturbed in both eyes, and will show a hemiopic or quadrantic form. The angiospastic amblyopias as a whole are not only of sudden onset, but tend to be of short duration, and are prone to recurrence. They also tend to affect both eyes sooner or later. Repeated small attacks of this kind, especially if the patient suffers from arteriosclerosis and hypertension, may be the forerunners of a fatal cerebral seizure.

Other examples could be quoted of sudden or temporary loss of vision due to deprivation of blood in different parts of the visual pathway. A very striking phenomenon, experienced for the most part in flying, is the "black out" of vision which occurs when the pilot changes direction or speed when coming out of a dive or looping the loop. In this case the mechanical factor is ischæmia of the visual centre, due, not to vascular spasm, but to draining of blood from the head vessels to the abdominal reservoir by the action of gravity. The whole of the vascular tree in the upper part of the body is involved.

A form of temporary amblyopia of rapid onset, which seems to be in no way related to vasomotor disturbance, is occasionally met with in *diabetes mellitus*, and may indeed lead to the diagnosis of that malady. The patient realizes that there has been a rather abrupt change in the vision, that distance vision is less clear and that reading is easier without glasses, that is to say, the eyes seem to have become myopic, and a refraction test confirms this. The phenomenon is due to a change in the refracting power of the crystalline lens, and with a change of glass the visual acuity may prove to be normal. After appropriate general treatment the refraction will return to its original state.

The examples quoted will serve to illustrate the variety of pathological conditions which may underlie the symptom of sudden or rapid failure of vision, and at the same time indicate the important part played in these conditions by the blood vessels of the visual pathway.

PROBLEMS OF ETIOLOGY

A precise knowledge of etiology is undoubtedly essential for the rational treatment of disease; but, fortunately for the credit of the profession, a good many eye diseases the cause of which is still unknown show a tendency to heal under the most simple forms of treatment. This applies particularly to acute infective diseases, in which the battle between the infective agent and the bodily defences is short and, as a rule, favourable to the latter. In another group, of apparently intractable cases, discovery of the cause, and the application of the appropriate treatment, lead to a prompt cure. Blepharo-conjunctivitis due to the *Morax diplobacillus*, staphylococcal infections of the lids, allergic reactions such as angioneurotic œdema, dermatitis from contact with certain plants, and the effects of irritants like industrial dusts and gases, are in this category.

The etiology of the *uveal inflammations*—iritis, cyclitis and choroiditis—is a wide and difficult field. Before the introduction of the Wassermann test there was a tendency to attribute most of these, as well as affections of the optic nerve, to syphilis. The acceptance of the Wassermann reaction as the criterion for the diagnosis of this disease narrowed down the field considerably, and the spirochæte yielded place to the tubercle bacillus as the villain of the piece. It is seldom easy to prove the tuberculous origin of these inflammations, but in many cases in which even the possibility of such an origin is assumed, specific treatment gives good results.

Focal sepsis, virus infections, bacteriæmia or toxæmia, and the exanthems are all capable of playing a part in the etiology of uveitis, and there must be few, if any, systemic diseases which have not included iridocyclitis or choroiditis among their clinical manifestations; but it must be admitted that in many cases the most thorough investigation fails to trace the cause. Among the more recently defined disease entities, Boeck's sarcoidosis and the deforming rheumatic disease, spondylarthritis ankylopoietica, may be referred to, since in both cases a subacute uveitis may be a feature of first importance, and either the physician or the ophthalmologist may be the first to be called upon for a diagnosis.

Cataract and maternal rubella.—An interesting puzzle in the etiology of ocular disease has recently come to the fore in South Australia, from the discovery of congenital cataract in children whose mothers had suffered from German measles during the early months of pregnancy. The study of over 150 cases shows that in the great majority the maternal rubella occurred during the first four months of the pregnancy; and a survey of the material available since 1941 shows that the problem is a larger one than the original observations suggested, for along with the congenital cataract a large proportion of the children had one or more of a number of deformities, such as buphthalmos, heart disease, deaf-mutism, talipes, mental deficiency, microcephaly. On the other hand, a variety of congenital abnormalities have been reported in the case of children whose mothers suffered from some other

exanthematous disease, for example, measles, mumps, chickenpox or scarlet fever, during pregnancy.

THE EYE AS A GUIDE IN DIAGNOSIS

In this section I shall confine my remarks to the help to be obtained by *ophthalmoscopic* examination in cases of systemic disease. There are two points which perhaps do not receive sufficient emphasis in the discussion of ophthalmoscopic diagnosis:—

(1) The components which make up any pathological fundus picture are few in number—hæmorrhages, exudates, vascular changes, and œdema or atrophy of the optic disc—but experience in the use of the ophthalmoscope permits the recognition in these of a multitude of variations of shape, size, number and distribution which supply the data necessary for differential diagnosis.

(2) No pathological condition of the fundus is static. The earliest stage of any such condition presumably consists of changes too small for ophthalmoscopic visibility, and the first visible lesions may differ so strikingly from those of the terminal phase as to be scarcely recognizable as stages in a single pathological process.

These points are well illustrated in the retinopathies of essential hypertension and diabetes mellitus.

In *essential hypertension*, uncomplicated by pre-existing arteriosclerosis, may be recognized an early stage in which the retinal vessels as a whole are well filled, tortuous and of good colour, the axial reflex of the vessels being so bright as to lend the vessels an appearance of a "copper wire". At this stage, too, the veins may show an apparent narrowing of calibre where they are crossed by the arteries. This stage may be described as the "fundus hypertonicus". If the patient's general state improves under treatment the condition of the fundus may return to normal, but in progressive cases there will appear sooner or later the features characteristic of malignant hypertension.

The first indication of this change is a general narrowing of the retinal arteries. Localized constrictions of the arteries may also occur, and so-called "nipping" of the veins at the arteriovenous crossings becomes more manifest. It is admitted that the narrowing of the arteries is due in the first place to spasm, giving place later to an organic, sclerotic process, but the transition from the spastic and functional change to the contracted lumen of arteriosclerosis is not at first marked by any visible alteration of the vessel walls. But with increasing evidence of failure of renal efficiency, and with signs of sclerosis of the renal, cerebral and peripheral vessels, the complete picture of hypertensive retinopathy gradually evolves.

The components of this picture, as already noted, include hæmorrhages, exudates and vascular changes, and papillœdema is often a feature, some-

times so pronounced as to suggest the presence of an intracranial neoplasm. The hæmorrhages are characteristically superficial, striate or spindle-shaped because of their situation in the nerve fibre layer, and grouped in the first place near the disc. Later on they become more widespread and may affect all layers of the retina. The exudates are of three types: small discrete punctate exudates which coalesce to form larger patches, scattered woolly white patches, and diffuse sero-fibrinous infiltration of the retina, especially round the disc. In the fully developed stage, punctate exudates group themselves centrally to form the "macular star" formerly considered typical of "albuminuric retinitis". The retinal vessels may or may not show evidence of sclerosis.

The hæmorrhages and exudates are so characteristic as to be almost pathognomonic of the disease, but in trying to assess the significance of the vascular conditions it must be remembered that the association of arteriosclerosis with hypertension is neither constant nor inevitable. Generalized arteriosclerosis is usually irregular in its distribution, and it may be present before the onset of hypertension or develop later as a complication of the disease, but usually in the final phase of malignant hypertension arterial changes—general narrowing, local constrictions, sheathing, obstruction, and new formation of vascular networks—form a notable part of the fundus picture, comparable changes being present in the cerebral and renal vasculature.

In *diabetes mellitus* the earliest recognizable fundus change is the appearance of minute red dots, usually near the macula, which the microscope shows to be aneurysms on the retinal capillaries. Hæmorrhages are a later development, and take the form of dots and blots of varying shapes and sizes. Many of these can be shown to consist of blood which has escaped by rupture or by diapedesis from the capillary aneurysms. The tendency of the hæmorrhages in diabetes to assume a round or polygonal form is due to their situation in the deeper retinal layers, in contrast with those of the hypertensive fundus, which are situated chiefly in the nerve fibre layer. Punctate exudates may be added to the micro-aneurysms of the first stage, and these, like the exudates of hypertensive retinopathy, tend to coalesce to form increasingly larger patches. In the diabetic fundus, as a rule, the patches assume a characteristic waxy appearance, with a faintly yellow colour.

Vessel changes in the diabetic fundus are peculiar in that they fall first, and most severely, on the veins. As a rule they appear in diabetes of long standing. In addition to a general tendency to fullness and tortuosity of the retinal veins, will be found sheathing of the veins, localized loops and kinks, and newly built vessel networks in and on the surface of the retina. Histologically these are represented by phlebosclerosis, phlebitis, fatty infiltration of vessel walls, and masses of newly built, thin-walled vessels like grossly enlarged capillaries. In the latest phase increasing exudate and large

intra-ocular hæmorrhages may cause detachment of the retina and other complications leading to blindness.

Thus, a comparison of the ophthalmoscopic features of hypertensive and diabetic retinopathies shows how the fine differences in the characters of these lesions give valuable aid in differential diagnosis, and the importance of recognizing the progressive nature of the clinical picture.

The ophthalmoscope in pregnancy.—It is common practice to make periodical tests of the urine and measurements of blood pressure in the course of pregnancy and, although it may be a counsel of perfection, there is something to be said for a routine ophthalmoscopic examination as a further check on the patient's general state, for the fundi may present fine but unmistakable changes, the knowledge of which would give early warning of some complication calling for special care or treatment. Thus, in the absence of any visual disturbance, and even in the absence of general symptoms, there may be early signs of hypertension, arteriosclerosis, nephrosclerosis or diabetes. The significance of the first of these is well known, and diabetes may be revealed, or aggravated, by the systemic disturbances of pregnancy.

Vomiting may be a distressing complication at any stage in pregnancy, but severe and persistent vomiting, which deserves the name of *hyperemesis gravidarum*, may be accompanied by fundus changes and a loss of vision which are of serious significance. In the gravest cases the patient is too ill to permit a careful test of the vision, but at an earlier stage it will be found that the visual defect takes the form of a central scotoma, due to a retro-bulbar neuritis, and fundus changes, if present, consist of hæmorrhages with perhaps a degree of papillædema.

In the pre-eclamptic type of toxæmia there may be a rapid and profound loss of vision with relatively slight fundus change, consisting of diffuse narrowing of the retinal arteries, some narrowing of the veins at the arterio-venous crossings, and slight œdema of the optic disc and retina. The presence, at the same time, of cotton-wool patches, hæmorrhages and organic changes in the retinal vessels will, of course, point to cardiovascular and renal complications.

THE EYE AS A GUIDE TO PROGNOSIS

The question of prognosis is closely linked to that of diagnosis, and the value of examination of the eyes in the assessment of prognosis is well illustrated in the conditions which have been considered in this article.

In *hypertension* the presence of the fundus hypertonicus (the "red hypertension" of Volhard) is consistent with the presumed absence of primary renal disease, and the absence of hæmorrhages and exudates suggests the possibility that the disease may be controlled by a suitable course of treatment. On the other hand, the addition of hæmorrhages and exudates, and

still more important of organic changes in the vessel walls, points to the development of malignant hypertension, with a notably unfavourable prognosis. The severity of the fundus changes is generally a fair indication of the gravity of the prognosis. At the same time it must be remembered that evidence from the fundi is only one contribution to the prognosis. Although there is generally a parallel development of vascular disease in the retina, kidney and brain, this association is not always consistent. An opinion regarding the outlook must be based on a knowledge of such other factors as blood pressure and renal efficiency.

A matter which perhaps deserves mention here is the state of the fundus after sympathectomy for hypertension. In a number of cases with pronounced hypertensive retinopathy a surprisingly complete disappearance of hæmorrhages and exudates has been observed. The significance of this in relation to the prognosis of the individual case is not yet determined, but it at least indicates that under certain conditions the retinal changes can be resolved in a way which is by no means common under non-surgical treatment.

The prognostic value of fundus changes in *diabetes mellitus* is unfortunately not so high as in the hypertensive diseases. The presence of diabetic retinopathy in a case described as mild and easily controlled is not uncommon and, on the other hand, the state of the fundi may advance to the point of causing blindness, in a reasonably healthy patient. The retinopathy itself shows a notably progressive tendency, and is not likely to improve.

In the special case of *pregnancy* it is sometimes possible by rest, medicinal treatment, and maybe the artificial termination of pregnancy, to restore vision and even to resolve the pathological condition of the fundus; but if the fundus lesions include organic changes in the retinal vessels, it is probable that after delivery there will be a permanent hypertension, with arteriosclerosis affecting the renal and peripheral as well as the retinal vessels. If a pregnant patient suffers from hypertension with retinal changes, and if significant improvement is not obtained within two weeks, termination of the pregnancy is unconditionally called for, since persistence of these disorders means a serious outlook for the health and vision of the mother, as well as for the life of the infant.

COLOUR BLINDNESS IN THE LIGHT OF RECENT THEORIES OF COLOUR VISION

By H. HARTRIDGE, M.D., Sc.D., M.R.C.P., F.R.S.

Director, Vision Research Unit, Medical Research Council.

MOST of us were taught during our medical training that colour vision is trichromatic, and that there are three types of receptor in the retina which are used for colour vision: a red type, a green type and a blue type. An individual having all three types has normal colour vision; one with only two types has dichromatic vision; whilst a person possessing but one type has monochromatic vision, which is equivalent to saying that he is completely colour blind. This very simple classification was soon found to require modification, because it was discovered that there are three types of individual having trichromatic vision. One of these, the normal trichromat, requires the usual amounts of red and green in order to match yellow; another type, the protanomalous trichromat, requires much more red to be mixed with the green in order to match yellow; and the third type, the deuteranomalous trichromat, requires much more green in the red-green mixture in order to match yellow.

TRICHROMATIC COLOUR VISION

These differences among trichromats are not easy to account for on the trichromatic theory. As their name suggests, the protanomalous trichromats are supposed to form an intermediate type between the protanopes on the one hand and the full trichromats on the other, that is to say, they resemble the latter in having trichromatic vision but they resemble the former in being markedly red-deficient. It is stated that it is because of this that they require more red than normal people do in order that a red-green mixture shall match a standard yellow. The deuteranomalous trichromats similarly, are supposed to be intermediate between normal trichromats and deuteranopes. It will be recollected that the deuteranope was defined as being green blind in the old days when colour blindness was first studied. The deuteranomalous trichromat therefore had some measure of green blindness although not so complete as that in the deuteranope. It was suggested that this deficiency of green reception would account for the fact that these subjects require a greater amount of green in a red-green mixture in order that it may match a standard yellow. Two comments may be made:—

In the first place, the deuteranope is no longer regarded as being green blind but is thought of as possessing both red and green receptors, resembling closely those present in the normal trichromat, with, however, this

essential difference, that in the latter each type of receptor has a separate nervous pathway which connects it with the brain, whereas in the deuteranope the red receptors and the green receptors are linked together and are connected to the brain by a single nerve path; thus these subjects are dichromats because they have only two receptor mechanisms, one responding to the long wave-length rays the other responding to the short wave-length rays of the spectrum, but they are neither red blind nor green blind because they have both active red and active green receptors. They cannot, however, distinguish red and green, because although the receptors would provide differentiation, they are interconnected so that they act as one type of receptor mechanism only.

The second comment concerns the validity of the argument that weakening of either the red or the green receptor mechanisms will affect a red-green mixture and not affect at the same time the yellow which it matches.

Suppose there to be two individuals A and B. In A the red receptors and the green receptors are equally sensitive, but in B the green receptors have only half the sensitiveness of the red ones. Suppose then that A makes a match between a pure yellow and a mixture of red rays and green rays, and that this match is then examined by B. Now B's green receptors have only half the effectiveness of A's green receptors, the consequence being that to B the red-green mixture looks less green than it does to A; but exactly the same argument applies to the pure spectral yellow, and this also must look less green to B than it does to A, because it stimulates B's green receptors less strongly than it does A's. On these grounds there is no reason to suppose that B will require a different proportion of red rays to green rays in order to match yellow, since both will be equally altered in the direction of red, and in consequence when a match has been made by A it should, on the basis of the three-colour theory, be accepted by B.

Now experiments with Raleigh's anomaloscope show conclusively that protanomalous trichromats actually do require more red, and that deuteranomalous trichromats similarly require more green in a red-green mixture which is being made to match a standard yellow. These differences cannot be accounted for satisfactorily on the three-colour theory. This is only one of the difficulties with which supporters of this theory find themselves confronted. Thus persons with normal sight find the pure spectral colours more saturated than mixtures of red rays and green rays or mixtures of green rays and blue rays, as the case may be, but this is not the case with anomalous trichromats, who find the mixtures and the spectral colours equally saturated. Three-colour theorists explain the difference in the case of subjects with normal colour vision by supposing that each of the fundamental sensations responds not only to its own particular part of the spectrum, but also to some extent to every other part as well, that is, that the response curves of the receptors are broad and lack selectivity. Anomalous trichromats who find the spectral colours and the mixtures which match them equally saturated must be supposed to possess receptors which respond to their own particular part of the spectrum and which do not respond to other parts as do those which are present in the retinas of subjects who have normal colour vision. It is therefore concluded that

anomalous trichromats have receptors with a higher degree of selectivity than those present in subjects who have normal colour vision. Now the better the selectivity the better the colour vision should be, and so it is concluded that anomalous trichromats have better colour vision than that present in subjects who have normal hue perception: but, in fact, the exact opposite is the case, and anomalous trichromats have greatly inferior colour vision to that of normal subjects, so that in this case also the three-colour theory leads to deductions which are at variance with the facts.

POLYCHROMATIC COLOUR VISION

Recently, as the result of improvements in the older methods of research, and owing to the use of entirely new methods, it is being found with increasing certainty that human colour vision is not trichromatic at all, but is polychromatic, depending not upon three types of colour receptor only, but on many types, possibly as many as seven. It seems likely that there is one for each of the named colours of the spectrum: red, orange, yellow, green, blue-green, blue and violet. This evidence may be summarized as follows: In the first place there are the researches of Professor Granit of Sweden, who has investigated the colour properties of the eyes of many animals by ascertaining the action potentials of the fibres of the optic nerve when rays of different colour and intensity are caused to fall in turn on the retina. Instead of finding only three types of receptor with relatively broad response curves he found several types which have somewhat narrow response curves which he called "modulators," and, in addition, a type having an exceptionally broad response curve which he called "dominators". The latter appear to be used for the appreciation of brightness, whereas the former are employed for the perception of colour. I endeavoured to perform similar experiments on man, making use of an instrument which is called a microstimulator. Essentially it is like a microscope, only used the reverse way round, so that instead of magnifying it diminishes and is thus able to produce points of light of extreme smallness. These are caused to fall on the retina in such a manner that single receptors or small groups of receptors are stimulated. This instrument has been used already for many types of investigation, and evidence of a reliable nature has been obtained for a polychromatic rather than a trichromatic arrangement of receptors. The theory based on these observations is able to account for many problems which the older three-colour theory was unable to do. Thus, on the older theory it was difficult to explain why the size of the visual field for pure spectral yellow, as measured by a perimeter, is very much larger than that for a mixture of red rays and green rays which matches the pure yellow as closely as it is possible in hue, brightness, and saturation. According to the three-colour theory red receptors and green receptors are stimulated by both yellows to the same extent. On the contrary, according to the polychromatic theory the pure yellow stimulates yellow receptors strongly and red and green receptors feebly, whereas the opposite

is the case with the red-green mixture. Thus supporters of the polychromatic theory can account for the differences in size of the fields for two yellows.

Another phenomenon difficult to account for on the three-colour theory are the changes produced in the appearance of the spectrum by adapting the eye to pure yellow rays on the one hand, and to a mixture of red rays and green rays on the other. In this case also there are difficulties in accounting on the older three-colour theory for what is seen, because both the yellows should stimulate red receptors and green receptors to the same extent, and thus should cause similar adaptation effects. But they do not do this.

Lastly, reference may be made to the directional effects of Stiles and Crawford. It will be remembered that rays passing through different parts of the pupil are found to produce different visual effects. There are differences of intensity, differences of hue and differences of saturation. Thus yellow has a different directional effect from either red or green, a fact which is difficult to account for on the three-colour theory, but is easy to account for on the polychromatic one, because it postulates that different receptors are used for the perception of monochromatic red, yellow and green. Returning to the matter of trichromatic vision, a provisional description, on the basis of the polychromatic theory, may be given as follows: The normal trichromat possesses all types of colour receptor and thus has the best possible hue perception. To him a pure spectral yellow is more saturated than a red-green mixture, because the former stimulates the specific yellow receptors whereas the latter does not. The protanomalous trichromat lacks many of these receptors and in a typical case is limited to three only, orange, green and blue. To him the yellow is inferior in saturation and is no better in this respect than a red-green mixture, because he does not possess the yellow receptors which are essential for the perception of yellow in its true purity. Edridge Green reported that some protanomalous trichromats call the yellow part of the spectrum "red-green" and describe it as looking a pale brown. The deuteranomalous trichromat has a type of colour vision apparently intermediate between that of an anomalous trichromat and a deuteranope; but they do not all fall into the same category, and further investigation will be required before a precise description can be given of their colour defects.

DIAGNOSIS

How, it may be asked, does this new approach affect the diagnosis of colour deficiency? Can we still usefully employ the methods of testing to which we have grown accustomed, for example, Ishihara's test or the lantern test, and may we continue to classify our patients as trichromats, dichromats and monochromats as we have done in the past?

It may seem strange at first sight that the answer to both these questions is "yes". The reason for this depends upon several facts which may be stated briefly as follows: The subject who has full colour vision and who therefore, according to the polychromatic theory, possesses seven different

types of receptor, depends to a very large extent upon three of these only for colour vision in average daylight for objects which subtend an angle of two or three degrees at the eye. It is true that four other types of receptor play a part, but it is only a minor part, making colour vision more vivid than it would otherwise be. Under other conditions the situation is quite different. Thus at very high light intensities or at very low light intensities important modifications in colour perception take place, but these do not ordinarily concern us when we are testing for colour blindness, neither are we usually concerned with the colour vision of the periphery of the retina, nor with test objects which subtend only a very small visual angle at the eye. Thus, in general, subjects with normal colour vision depend principally upon three types of receptor for their ability to recognize colours, and the same statement is true of the two other types of trichromat mentioned. Since they can recognize without difficulty three essentially different colours in the spectrum—red, green and blue—they do not ordinarily confuse the colour of signals to such an extent that life is endangered.

What then is the position of the dichromats? According to the polychromatic theory they possess only two of the three essential types of receptor, and therefore confuse, or are very liable to confuse, either reds with greens or greens with blues. Those who make the latter confusion are seldom dangerous because the differentiation of greens and blues is not ordinarily required in colour signalling, but those who confuse reds and greens are highly dangerous and must be identified lest they should cause harm to the community. The same statement applies to the monochromats who, as already stated, are completely devoid of all colour perception. The older classification may therefore stand without alteration, and persons who make no mistakes with signalling lights may be called "trichromats"; those who confuse red with green or blue with green "dichromats"; and those who confuse them all "monochromats"; just as before it became evident that human colour vision is in fact polychromatic.

What then is the situation with regard to the tests for colour vision? The answer is that they require no modification. They were able to differentiate precisely between those who were dangerous and those who were not. This is still the essential criterion so far as practical sight testing is concerned, so that the old colour vision tests may still be employed, with satisfactory results. But, if we are not concerned solely with the presence or absence of danger, and are inquiring into the character of man's colour vision, then other more exact tests are required. It is necessary to use a spectroscopic test, such as Dr. Wright's colorimeter, not only under average conditions of illumination and field size, but also at the extremes of illumination both high and low, and also for field sizes both large and small. When this is done the polychromatic nature of man's normal colour sense amply reveals itself. In fact, it would not be too much to say that there is no longer a single phase of normal colour vision which does not disclose in a clear manner the essentially polychromatic nature of normal colour vision.

THE CAUSATION AND TREATMENT OF DETACHMENT OF THE RETINA

By FRANK W. LAW, M.D., F.R.C.S.

Ophthalmic Surgeon, Guy's Hospital; Surgeon, Moorfields Eye Hospital.

THE introduction of a reliable method of treatment of detachment of the retina carrying a large percentage of cures is one of the most gratifying advances which the present generation of ophthalmologists has experienced. The condition is by no means uncommon, and before Gonin, by introducing cautery puncture, started the interest in, and research into, operative treatment which has resulted in the present-day technique, all that was done was to lay the patient flat in bed and, by giving "absorptive" drugs by mouth, hot-air baths, and mercury inunctions, ostensibly to encourage absorption of the sub-retinal fluid. It is true that a small number of retinæ did become replaced after such a spell of treatment, but it is permissible to doubt whether these would not have done so spontaneously, without any treatment or immobilization of the patient at all. The treatment was inadequate in that it ignored the fundamental point in the pathology of the majority of cases, i.e., the hole in the retina.

Before going into causation in detail it is well to point out that the very term "detachment of the retina" is a misnomer. This term implies that the retina becomes detached from the next membrane, the choroid, leaving a fluid-filled space between these two, the one ectodermal in origin, the other mesodermal. Such, however, is not the case. The retina splits into two moieties, the nervous layer within and the pigment layer without, with the fluid lying between the two; and there is an excellent embryological reason for this, since it represents a separation of the two membranes derived from the original two layers of the (ectodermal) secondary optic vesicle. Separation of the retina would thus be a more justifiable term, and the fluid would be more accurately described as inter-retinal. The popular term, however, is unlikely to be displaced, and it is interesting to note that the misnomer is repeated in many other languages (*décollement de la rétine: desprendimiento de la retina: netzhautablösung*).

A few types of detachment of special origin may be mentioned before considering the common variety. The presence of a choroidal neoplasm which grows centripetally, as most do, will clearly tend to lift the retina from its bed and, by accumulation of fluid, cause further separation at a distance from the site of the original cause. Indeed, the presence of this so-called secondary detachment is a most important feature in diagnosing a fundal swelling suspected of being a choroidal neoplasm. Another cause of detachment is found in toxic hydropic conditions, such as eclampsia,

toxæmia of pregnancy, and renal disease. Recently I was asked to see a case of hypertension with renal failure in which there was complaint of loss of vision. It was found that the lower halves of both retinae were detached in balloon fashion. Such serous detachments commonly subside with the amelioration of the general condition.

CAUSATION

The common type of detachment arises as a result of a combination of factors, but with one probably fundamental, as has already been indicated. The average age is somewhere in the neighbourhood of fifty; the sex distribution about 60 per cent. male and 40 per cent. female. The *refractive error* is of importance, something like two-thirds of the cases being myopes; it does not appear that the degree of myopia has much influence on occurrence, but since there are more moderate myopes than high myopes a higher proportion naturally occurs in this group. About a quarter of the cases are hypermetropic, the rest being approximately emmetropic.

It was Gonin's appreciation of the importance of the *hole in the retina* which led to his evolving the cautery puncture method of treatment. Although it is still impossible in a small minority of cases to find a hole, there are good grounds for believing that its presence is fundamental and constant. It is easy to understand that a hole may be difficult to see even if in view; it is equally obvious that a hole may be hidden behind a fold or mound of retina; and if one decides to operate on a case in which no hole has been identified—a rare occurrence—it is with grave misgivings as to the possibility of success. The most common site for a hole is in the upper temporal quadrant; the upper nasal and lower temporal come next, whilst few are found in the lower nasal quadrant; 90 per cent. or so are found anterior to the equator of the globe, and more than one is found in a quarter of the cases. About half of the holes are horse-shoe shaped or "arrow-head"; a third are round, and the rest are oval or linear, crescent-shaped, or irregular. In 10 per cent. of cases the ultimate cause of the detachment is found to be a tearing away of the retina at the ora serrata—the anterior area where it ceases to be functioning retina and merges into the pars plana of the ciliary body; more correctly referred to as an anterior retinal dialysis, this condition is popularly and loosely called a "disinsertion". It must be noted that these figures refer to a whole series of detachments; the variations are great when the characteristics of the hole are considered in relation to the different refractive groups.

The importance of a *pathological vitreous* is becoming increasingly recognized. The study of this medium has recently been greatly facilitated by the designing of a piece of apparatus which enables minute inspection under high magnification to be made; examination under these conditions reveals changes, such as separation and organization, which make it certain

that traction on the retina can and does occur. Confirmation of this possibility is found in the fact that, in many cases of horse-shoe rent or arrow-head tear, the free tag of retina is nearly always directed centrally, and is often seen to project into the vitreous. It is interesting to note that the tear is by no means always in the deepest part of the detachment; it may indeed be found in an apparently attached area of retina, the inter-retinal fluid having gravitated downwards, causing deep separation below. In a recent review of 100 cases of detached retina, such pathological vitreous changes were reported in 35 per cent. of cases.

The retina itself may be the site of the determining cause of detachment. *Degenerative changes* are by no means uncommon in this membrane, especially in the periphery, and if these changes proceed to actual solution of continuity, the stage is set for fluid separation. *Inflammatory lesions* of choroid and retina may lead to a similar result, the hole formation often being delayed for a long time after the active inflammation is past.

It is clear that *trauma* plays a part, although it is difficult to determine the extent to which this operates. It is never difficult for the patient to think of some degree of trauma in the past, however mild, and it is usual for such an explanation on his part to be forthcoming; it is, however, doubtful if moderate trauma uncomplicated by hæmorrhage often causes detachment in an otherwise normal eye. It is further important to note, as Shapland pointed out in the *British Journal of Ophthalmology* in 1934, that trauma plays a decreasingly frequent part in the etiology as the degree of myopia increases. Thus in myopia, spontaneous detachment is more usual; in emmetropia, trauma is more frequent, and severe direct injury is relatively less often an etiological factor than indirect or less severe injury. Consideration of these facts leads to the conclusion that minor injury may often well be the final cause of a detachment, but that a previous predisposing pathological state in retina or vitreous is likely in a majority of cases.

DETACHMENT IN APHAKIA

Detachment of the retina occurring after removal of the lens presents a more difficult problem both in pathology and treatment. It is by no means certain that the increasing popularity of the intra-capsular method of removal of cataract in the adult is more likely to lead to detachment than the older extra-capsular method; it is a fact that the removal of soft cataract in the young is followed by this complication in later life in a disturbing number of cases. The practice of removing the lens for high myopia in children has been discontinued, largely, it seems, on account of the frequency of this occurrence.

In a considerable proportion of cases of detachment in aphakics no hole can be found on examination; the importance of this fact has already been emphasized. Examination of the fundus in aphakia, especially after extra-

capsular extraction, is admittedly far more difficult than in the eye with the lens *in situ*; it is, however, probable that the high proportion of detached retinae in such cases which possess no hole is real and not apparent only. Further, the distressing fact remains that, whether a hole is found or not, the operative results in aphakia are much worse than in the normal run of cases, many relapsing into detachment a few weeks or months after operation, even if immediate reposition appears to have occurred, which is by no means universal.

SYMPTOMS

The characteristic history is the complaint by a patient of a cloud or veil over part of the field of vision, typically peripheral. This may have been preceded by flashes or sparks or other subjective entoptic phenomena, and such occurrences may provide valuable indication of the possible site of the hole, and guide the surgeon in his search for it. An increase in the size of the obscured part of the field is an indication for urgency in immobilization and operation, especially if the affected area is noticed to be approaching the fixation point.

TREATMENT

Excluding a few numerically negligible cases, the treatment of detachment of the retina is operative. Reference has already been made to the secondary serous detachments which do not need treatment because of their almost invariable tendency to automatic replacement. There are further, a few cases of shallow detachment in the lower temporal periphery arising from an anterior dialysis, which it is the custom of some surgeons to leave alone, in the knowledge that many of these are congenital in origin, and in the hope that the condition will not alter. Experience compels me to admit that many of these detachments are present for a long time before discovery; this constitutes a justification for a waiting policy, although in my view a preventive operation is the proper course.

It is justifiable to repeat that the determining factor in treatment, and the one upon which the prognosis most heavily depends, is the hole in the retina. Sometimes this is obvious at first glance; then, providing adequate search has been made to exclude so far as possible the presence of more than one hole, operation may be confidently undertaken. If the detachment is deep, or if other factors, such as a cloudy vitreous, suggest that the hole may well be present though invisible, the proper course is to submit the patient to strict recumbency for a few days, to allow the vitreous to clear and the retina to settle back more nearly into place, when often a further search is repaid by success. Many adopt this preoperative routine in every case, even when a hole has been found, since the chances of operative success are enhanced by closer apposition of retina and choroid at the time of operation.

Gonin's operation.—As has been mentioned, Gonin introduced the idea of sealing the hole in the detached retina by means of a cautery puncture thrust through the sclera and choroid in such a position as to seal the edges of the hole. The difficulties of such a manœuvre need no comment; the operative results when the "bull's eye" was hit were excellent, thus justifying the rationale and leaving nothing more than to find an easier way to achieve the desired result, i.e., the obliteration of the hole. The first operation of this type was performed in this country in 1929; in a series of 221 cases thus treated, 30 per cent. were cured and 10 per cent. improved. The term "cure" is used to mean complete reposition of the retina without reference to the visual result; the reason for this will be referred to later.

Guist-Lindner's operation.—The next stage in the simplification of operative procedure consisted in the introduction of the multiple trephining method of Guist-Lindner. Here the necessity of dealing with the actual hole in the retina was circumvented; many trephine holes were made in the area of the hole reaching down to, but not perforating, the choroid, and a caustic was applied to the choroid to cause a chemical reaction, so that on releasing the sub-retinal fluid the adhesions between the retina and choroid isolated, and thus effectively sealed, the hole. This method gave about 25 per cent. cures and 15 per cent. improved. The operation was technically very difficult and most tedious to perform, and the aim of causing adhesions over a wide area in the neighbourhood of the hole, relieved of the necessity of striking the hole accurately, has been achieved by the use of the *diathermy current*. It must not be supposed that it is immaterial how much reaction is caused; the result must be to cause the minimum, since any retinal area thus affected is necessarily functionless. Diathermy, however, enables the operator to create an area of reaction *in an intact globe*, to examine the fundus and see the relation between the area and the hole, and to adjust the subsequent applications so that the hole is accurately surrounded by reaction.

The anæsthetic employed may be local, or a non-inflammable general. Locally, pantocaine is used for the cornea and conjunctiva, as it is less liable to cause corneal haze and interfere with inspection. A retrobulbar injection of novocain, 2 to 4 per cent., is essential, and if given carefully is unlikely to cause retrobulbar hæmorrhage. The indifferent electrode is strapped to the wrist over a special "contact paste"; the active electrodes vary in size, shape and design to suit different needs, and are insulated right up to their ends. A conjunctival flap of suitable size and position is laid back, and the area of sclera concerned is exposed; any bleeding point is touched with the cautery. If desired, one or two recti muscles may be divided at their insertion and resutured after operation in order to give better exposure—a procedure which causes no ill-effects. The "area of sclera concerned" is of course determined by the position of the hole on ophthalmoscopic examination; the accurate charting of distance from limbus, and meridian, and surface-marking the sclera, has become obsolete with the change in type of operation, and in any event it was virtually impossible to determine just where a hole seen in a deeply detached retina would fall on the choroid after release of the sub-retinal fluid. A metronome is set going to beat seconds, and the instrument is adjusted to give a current of about 75 milliamperes; the electrode is applied to the sclera and the circuit closed by the surgeon's foot switch for 10 seconds. My habit is now to examine the fundus to see the density of

reaction and its relation to the hole; adjustment of current and site of application is made and sufficient contacts to ensure that the hole is ringed by reaction; the white fluffy appearance is unmistakable, and the nearer to the edge of the hole it is made the better. The electrode is changed for a sharp needle, and the circuit is closed before application so as to cause a spark. Perforation is ensured in one to three positions, and the sub-retinal fluid sucked out mechanically.

The collapsed appearance of many eyes after this treatment would cause many an inexperienced observer misgivings, but recovery of normal tension follows in a few days.

The patient is put back to bed in such a position that the punctures are situated as nearly as possible in the most dependent part of the globe to ensure drainage; it is doubtful whether this occurs after a day or two, and some surgeons deny its importance and ignore the question of position, relying upon absorption of the remaining fluid. Absolute rest for fourteen days is the routine; the eye need not be dressed for three to four days and should not be closely examined for a week. It is the custom in this country to allow little movement before three weeks have elapsed; a change of position is allowed in the third week to a more normal one if the hole was in an awkward position. Stenopæic spectacles ("pinholes") to restrict eye movements are given a day or two later, and the patient is allowed up about the twentieth day. More experience is required in order to allow possible revision of this most tiresome programme; immobile recumbency with both eyes bandaged for two weeks or more is a great strain to any patient and impossible to some. In doubtful cases one is not exercised as to the correctness of the procedure; it is those which look obviously successful or obvious failures at the end of a week which cause the worry—is it safe to curtail convalescence for the former, or a waste of time, patience, and bed space to prolong it for the latter?

Percentages of successful results after diathermy vary from surgeon to surgeon according to his attitude towards the general run of detachment. The one who carefully chooses his cases, and is prepared to tell the patients that their operative chances are hopeless if they are merely not good, will show better figures than the surgeon who is prepared to have a "sporting" attack—at the patient's request and with his full cooperation and understanding—at any but the truly hopeless. Uncomplicated anterior dialysis cases should show 100 per cent. success; uncomplicated recent shallow detachments with healthy retinae and well-defined hole or holes give almost equally good results; the results are worse with long-standing cases, degenerative retinae, and increasing myopia. I have yet to achieve a permanent success in an aphakic case. A generous surgeon will certainly obtain 50 per cent. successes in a complete series, and 60 to 70 per cent. is a generally accepted figure. A recent review of 100 cases from America gave 86 per cent. cured, but selection was not mentioned and no aphakic cases were included.

PREOPERATIVE CONSIDERATIONS

Apart from the hole, the important preoperative considerations are length of history and state of the retina. If the macula is detached, restoration of good central vision is unlikely if the detachment is more than eight weeks old, although it must not be supposed that restoration of central vision is the only object aimed at in operation. Return of valuable peripheral field may be expected after a long period of detachment; I recently operated successfully on a detachment caused by a flying-bomb injury, to the complete satisfaction of the patient. A non-visual aspect, but one none the less worthy of attention, is the fact that eyes with detachments are liable to degenerative changes which may cause pain or unsightliness avoided by operative replacement of the retina. Broadly speaking, only total detachments with degenerate retinæ may justifiably be denied the chance given by at least one operation. And persistence may even be rewarded after failure; a sixth attempt was successful in the only eye of a girl who now, twelve years after, has still useful vision and leads a normal life.

TREATMENT OF FAILED CASES

In conclusion, reference should be made to an operation which is being practised in cases which have failed to respond to the usual treatment, such as aphakics and high myopes. A strip of sclera in the pre-equatorial zone is excised over an area of about half the globe at one sitting; complete circumferential excision may be undertaken in two. The object is to shorten the antero-posterior axis of the globe and thus assist the retina, by closer apposition, to adhere to the choroid. The technique is moderately difficult, needing time and care. The enthusiasm shown for the operation at its initiation is waning, and more experience will have to determine its true value.

PENICILLIN IN OPHTHALMOLOGY

By ARNOLD SORSBY, M.D., F.R.C.S.

Research Professor in Ophthalmology, Royal College of Surgeons, and Royal Eye Hospital.

FEW drugs are as grossly abused as is penicillin in the treatment of eye disease. It is fortunate that penicillin is as harmless in abuse as it is effective in rational use. The effective use of penicillin requires in the first place a clear and accurate diagnosis of a susceptible infection, and secondly, an equally clear and accurate appreciation of dosage and modes of application. The fact that penicillin abused is harmless is only a partial truth: it is harmful in so far as possible therapeutic results from its full exploitation are not obtained by its inadequate use, and that when used in conditions in which it is not effective better methods of treatment are left in abeyance.

THE DIAGNOSIS OF INFECTION

The first step in the use of penicillin is therefore the diagnosis of infection. For practical purposes, so far as the practitioner is concerned, the infective conditions are confined to the outer eye. An intra-ocular infection generally runs a fulminating course, and even in the hands of the expert these infections still give poor results, as usually they are not diagnosed sufficiently early for penicillin therapy to be effective. The infections of the outer eye fall into several clearly defined conditions:—

(1) The classical purulent conjunctivitis seen in infants (ophthalmia neonatorum) and occasionally also in the adult. These acute purulent reactions present no difficulty in diagnosis, and early and adequate treatment is imperative if the sequelæ of corneal complications are to be avoided.

(2) Muco-purulent conjunctivitis, likewise readily diagnosed, but when it is confined to one eye the possibility that it is secondary to an infected lachrymal sac must be considered.

(3) Multiple or recurrent styes on the lid margins, also easy to diagnose.

(4) An infected lachrymal sac with an acute abscess formation, which again presents no difficulty in diagnosis.

(5) Less acute infections are represented by such entities as blepharitis.

In all these conditions penicillin used adequately gives excellent results.

Non-infective lesions.—Every inflamed or irritable eye, however, is not necessarily an infected eye. If they have done nothing else, the sulphonamides and penicillin have compelled a reassessment of classical diagnoses, many of which are anatomical rather than etiological. Not every case of "blepharitis"—which is merely bad Greek for inflamed lid margin—

is infective in type. An inflamed lid may be the result of constant rubbing of the lid, or of a drug irritation, or a secondary phenomenon arising from a non-infective conjunctival reaction. Nor is every case of conjunctivitis infective. The conjunctiva can become inflamed from other causes than infection, as in Spring catarrh, which is an allergic reaction, or in atropine irritation, which is a drug reaction. The inflamed conjunctiva in phlyctenular ophthalmia is the response of the conjunctiva to an endogenous irritation rather than to an infective agent. Likewise, corneal lesions are not always infective in origin. The lesion in corneal dystrophy is congenitally determined; that seen in acne rosacea or in phlyctenular keratitis is endogenous in character. The corneal lesions seen in epidemic keratoconjunctivitis are probably infective in origin, but the infective agent is a virus of the herpes group, which is not susceptible to penicillin. These examples could be multiplied almost indefinitely, and they serve to emphasize the fact that the first step in the use of penicillin is the diagnosis—diagnosis being not the use of an anatomical label, but establishing the fact that the condition is an infection due to a penicillin-sensitive organism.

The etiology of many inflammatory affections, such as the common conditions of iritis and iridocyclitis, is unknown. The temptation to use penicillin for such ill-understood entities may have justified experimental trial, but as such trials have proved negative there is no justification for the use of penicillin in practice. The recognition of these limitations has narrowed the field of penicillin therapy to a few clearly defined clinical entities. When these are diagnosed, the use of penicillin is not only justified but imperative. For other conditions it is just as imperative that penicillin should not be used.

MODE OF USE OF PENICILLIN

Adequate concentration of penicillin at the site of the infection is essential. So far as the outer eye is concerned, local approach is so easy that systemic administration is both unnecessary and wasteful; it is probably also less efficient. For infections of the lids and conjunctival sac, drops and ointments are adequate. Several considerations have, however, to be borne in mind.

In the case of *drops* it is necessary to appreciate the fact that all drops put into the conjunctival sac are washed out very quickly. This is clearly seen when such staining agents as fluorescein drops are instilled. Within a matter of a minute, staining has worn off, the agent having been washed out by the constant, even if imperceptible, flow of tears. To instil penicillin drops at intervals of three hours therefore implies treating the infective lesion for something like a minute and leaving it untreated for the rest of the time.

Ointments have the advantage that they stay in the conjunctival sac much longer than drops. From the therapeutic point of view they are drops in semi-solid form. This, however, carries a significant disadvantage. Whereas penicillin in watery solution has free contact with the infected surface,

penicillin in ointment form imposes a greasy barrier between the active agent and the infected surface. In severe infections this is an important limiting consideration; in less severe infections it matters little, provided the concentration of penicillin in the ointment base is sufficiently high.

If ointments may be regarded as something like solid drops, *subconjunctival injections* can be considered as self-retaining drops. If a solution of penicillin is injected underneath the conjunctiva it tends to be held in the potential subconjunctival space by the tense conjunctiva, instead of being washed out, as drops are, from the open conjunctival sac. Subconjunctival injections have a place in the treatment of corneal infections, and in infections of the anterior chamber.

Optimum concentration is determined by the nature of the infecting organism. Some organisms are readily susceptible to penicillin; others are fairly resistant. In practice, drops containing 1000 units of penicillin per ml. are adequate for gonococcal and staphylococcal infections, but inadequate for purulent conjunctivitis due to various bacilli, or pyogenic large-sized viruses. As the organism is not always known when treatment is most urgent, it is safest to assume a highly resistant rather than a highly sensitive organism as the cause. For this reason a concentration of 10,000 units per ml. is best. Ointments in such affections are not particularly satisfactory, and for the milder infections in which they can be used it would appear that a concentration of 1000 units per g. is adequate. When subconjunctival injections are used the urgency of the condition (a corneal infection or anterior chamber infection), as also the relative impermeability of the cornea to penicillin, dictates exceptionally high doses. Subconjunctivally, injections should carry 1,000,000 units of penicillin in 1 ml. of water, or preferably 0.5 ml. water and 0.5 ml. of adrenaline, as vasoconstrictors help absorption into the interior of the eye.

OPHTHALMIA NEONATORUM

Intensive local penicillin treatment gives highly gratifying results. The following procedure has been evolved at the Ophthalmia Neonatorum Unit at White Oak Hospital, where some four hundred infants have been treated with different methods of penicillin therapy.

(a) On admission a swab is taken for smear and culture and the eye is irrigated with half-normal saline at room temperature. A drop of adrenaline, 1:1000, is instilled, and a scraping is taken from the palpebral conjunctiva for examination for the presence of inclusion bodies. Atropine sulphate drops, 1 per cent., are instilled if the cornea is involved.

(b) Any pus that may have accumulated is wiped away with moist pledgets of cotton-wool, and 2 drops of penicillin, in a concentration of 10,000 units per ml., are instilled.

(c) The baby is now placed on the nurse's lap, while another nurse sitting

nearby instils 1 drop of the penicillin solution every minute for thirty minutes. Irrigation is not needed, for pus does not form to any extent; such thin mucoid discharge as is present can be ignored or, if it clings to the lid margin, wiped away with moist pledgets of cotton-wool.

(d) At the end of this time there is no pus and generally little or no discharge. The eye, however, is still moist, the lids are still swollen, and the lid margins tend to be sticky. The baby is returned to its cot and instillation of penicillin drops is continued six times at five-minute intervals, followed by a similar number of instillations at half-hourly, hourly and two-hourly intervals. This gives a total of 22 hours' treatment. Many cases require no further attention.

In some babies the lid margins still tend to be sticky. It is advisable in such cases to continue with penicillin at two-hourly intervals until the eye is dry, when treatment is still continued for a further twelve hours.

Relapses and unsatisfactory responses.—When relapses occur, it is only exceptionally that the condition is as severe as it was initially; generally an eye that had shown clinical cure either becomes moist or shows sticky lid margins. In such cases a further course of local penicillin usually clears the condition, suggesting an activated latent infection rather than a condition which is the result of mechanical handling. The possibility of re-infection also arises.

In contrast to relapses there are the cases with an unsatisfactory response—unsatisfactory in so far as there are persistent moistness of the conjunctiva and sticky lid margins, with occasionally a certain degree of œdema of the fornices. In no case should complications develop after admission, and in cases admitted with a hazy cornea, the eye rapidly returns to normal.

Response in relation to severity of the infection.—Severity itself is not a significant factor in the duration of treatment. Frequently, mild cases take longer to clear than do moderate or severe cases, and equally often severe cases show remarkably gratifying response within a very short time, the sensitivity of the infecting organism to penicillin rather than the severity of the reaction determining the course.

CONJUNCTIVITIS

Purulent conjunctivitis in adults.—This differs in no way from ophthalmia neonatorum, and treatment can be carried out on the same lines.

Mucopurulent conjunctivitis.—When due to a penicillin-sensitive organism rapid cure is obtained by the instillation of penicillin ointment, 1000 units per g., at two-hourly intervals for two to three days. It is desirable to continue applications at four-hourly intervals for forty-eight hours after clinical cure, in order to prevent a relapse.

BLEPHARITIS

When blepharitis is secondary to an acute conjunctivitis due to penicillin-

penicillin in ointment form imposes a greasy barrier between the active agent and the infected surface. In severe infections this is an important limiting consideration; in less severe infections it matters little, provided the concentration of penicillin in the ointment base is sufficiently high.

If ointments may be regarded as something like solid drops, *subconjunctival injections* can be considered as self-retaining drops. If a solution of penicillin is injected underneath the conjunctiva it tends to be held in the potential subconjunctival space by the tense conjunctiva, instead of being washed out, as drops are, from the open conjunctival sac. Subconjunctival injections have a place in the treatment of corneal infections, and in infections of the anterior chamber.

Optimum concentration is determined by the nature of the infecting organism. Some organisms are readily susceptible to penicillin; others are fairly resistant. In practice, drops containing 1000 units of penicillin per ml. are adequate for gonococcal and staphylococcal infections, but inadequate for purulent conjunctivitis due to various bacilli, or pyogenic large-sized viruses. As the organism is not always known when treatment is most urgent, it is safest to assume a highly resistant rather than a highly sensitive organism as the cause. For this reason a concentration of 10,000 units per ml. is best. Ointments in such affections are not particularly satisfactory, and for the milder infections in which they can be used it would appear that a concentration of 1000 units per g. is adequate. When subconjunctival injections are used the urgency of the condition (a corneal infection or anterior chamber infection), as also the relative impermeability of the cornea to penicillin, dictates exceptionally high doses. Subconjunctivally, injections should carry 1,000,000 units of penicillin in 1 ml. of water, or preferably 0.5 ml. water and 0.5 ml. of adrenaline, as vasoconstrictors help absorption into the interior of the eye.

OPHTHALMIA NEONATORUM

Intensive local penicillin treatment gives highly gratifying results. The following procedure has been evolved at the Ophthalmia Neonatorum Unit at White Oak Hospital, where some four hundred infants have been treated with different methods of penicillin therapy.

(a) On admission a swab is taken for smear and culture and the eye is irrigated with half-normal saline at room temperature. A drop of adrenaline, 1:1000, is instilled, and a scraping is taken from the palpebral conjunctiva for examination for the presence of inclusion bodies. Atropine sulphate drops, 1 per cent., are instilled if the cornea is involved.

(b) Any pus that may have accumulated is wiped away with moist pledgets of cotton-wool, and 2 drops of penicillin, in a concentration of 10,000 units per ml., are instilled.

(c) The baby is now placed on the nurse's lap, while another nurse sitting

Treatment should be essentially by systemic injection. For an adult, 2,000,000 units a day should be given in a single dose. Such massive doses may give an adequate intra-ocular level of penicillin, and they should be continued for at least ten days. They should be supplemented by sub-conjunctival injections, 1,000,000 units in adrenaline and water at intervals of forty-eight hours.

ACUTE DACRYOCYSTITIS

This generally requires incision and drainage. Local penicillin treatment is not quite so convenient as general sulphonamide therapy, which is the method of choice.

SOME PRECAUTIONS

It should not be necessary again to repeat that penicillin used in unsuitable conditions can only lead to disappointment. The value of penicillin is such that it is well worth while paying attention to every detail, and the following are points to be remembered:—

(1) All penicillin used in eye conditions should be crystalline (pure penicillin). The yellow amorphous penicillin contains variable amounts of impurities, some of which are highly irritating to the conjunctiva and cornea.

(2) The base of penicillin ointments is also of importance. Many bases are irritating and some do not liberate penicillin. A satisfactory ointment containing penicillin in suspension is one prepared of petroleum jelly and liquid paraffin, 90 and 10 parts of each respectively, into which the penicillin has been incorporated in solid form. Such ointments made with crystalline penicillin are stable over many months at room temperature.

(3) On no account must yellow amorphous penicillin be used for sub-conjunctival injections.

The use of penicillin in ocular infections has demarcated sharply the non-infective varieties of ocular inflammation from those due to infection. Only he who can free his mind from obsolete pathological conceptions is able to use effectively the therapeutics of a new age.

sensitive organisms, the blepharitis clears rapidly on treating the conjunctivitis, without any special attention being paid to the lid margins. This is seen typically in cases of acute staphylococcal conjunctivitis with a reactionary blepharitis. In the more common type of blepharitis, with its chronic course and no associated conjunctivitis, penicillin ointment, 1000 units per g., applied two or three times a day to the lid margins, generally produces a clinical cure within a fortnight or so. Before applying the penicillin ointment the lid margins should be cleansed of all crusts by the use of bicarbonate solution, which itself is then washed off with water.

Although blepharitis is readily ameliorated, relapses are, however, common, as often the underlying general condition is unsatisfactory, and this requires the usual measures against debility.

INFECTED CORNEAL ULCER WITH HYPOPYON

As in ophthalmia neonatorum, high concentration and constant application are essential. Subconjunctival injection makes this possible, so that frequent instillation of drops becomes unnecessary, whilst the use of penicillin in adrenaline enables a particularly high and sustained concentration in the cornea and aqueous to be attained. For the present, treatment of infected corneal ulcer is on these lines:—

(a) A conjunctival swab is taken for bacteriological examination.

(b) The pupil is kept dilated with atropine.

(c) Subconjunctival injection of penicillin (1,000,000 units dissolved in 0.5 ml. of water, and 0.5 ml. of adrenaline 1:1000) is given at intervals of forty-eight hours. Generally two injections are adequate, but more may be required. In severe cases with much hypopyon, injections at intervals of twenty-four hours may be advisable. The adrenaline may be replaced by 2 per cent. procaine. This ensures some analgesia, but care should be taken first to dissolve the penicillin in water, as the procaine will prevent crystalline penicillin from being dissolved.

(d) When the infection is under control, as shown by the disappearance of the hypopyon and clearing of the corneal infiltration, the subconjunctival injections are replaced by penicillin ointment, 100,000 units per g. instilled at four-hourly intervals, in order to consolidate the cure.

Usually three days' treatment with subconjunctival injections, and three or more days of treatment with ointment, should clear a hypopyon ulcer. The end-results are excellent. If, after twenty-four hours' treatment, there is no marked improvement, it may be taken that the infecting agent is not penicillin sensitive.

INTERSTITIAL KERATITIS

Judging by the response obtained in twenty-four personally observed cases, penicillin therapy has a definite place in the treatment of interstitial keratitis.

than by using the vergence amplitude. To begin with, this active suppression of what the squinting eye is looking at depends upon the straight eye fixing on the principal object. If the straight eye is covered the squinter will still be able to look at an object and see it reasonably clearly. As time goes on, however, the condition becomes more fixed, and *amblyopia* develops.

SPECTACLES AND OCCLUSION

It is obvious then that it would have been better to correct the hypermetropia with glasses as soon as possible after a convergent squint had started. Glasses may do all that is necessary to prevent the eyes assuming a permanent condition of over-convergence.

If amblyopia is present, however, the good eye will have to be covered and the child made to use the poor one. To be of value, such occlusion must be maintained constantly throughout the child's day, as doing without it for a time will allow him to bring about active suppression again. In marked degrees of amblyopia it is necessary to stick the occluding material down to the skin beyond the orbital margins, leaving only a gap temporarily for air to pass without the eye seeing through it. As the child becomes more accustomed to using the bad eye he should be less desirous of peeping with the good one past its occluder. A less drastic method can then be substituted—an appliance fixed to the spectacles or paper gummed to the one glass. The aim is to bring the visual acuities of the two eyes as near to equality as possible and then to get the two eyes to work together without suppression in either. In regard to the latter, it may happen when the original "bad eye" has improved and learnt to fix on objects, that with a tendency to over-convergence still present, the original "good eye" now squints in and may in turn suppress and even become amblyopic.

ORTHOPTICS

At this stage orthoptic supervision becomes advisable. An attempt may be made to assess more particularly the state of binocular vision. (The child may not yet be intelligent enough to do and say what is needed, so that orthoptic training must wait until he is older.)

The tests consist essentially of presenting a picture to each eye separately but simultaneously, and finding from the patient whether he is able to combine them. The simplest of all will be a pair of pictures having no parts common to both; for instance, a toy soldier for one eye and his sentry box for the other, no part of the sentry box appearing in the soldier picture, and *vice versa*. If the brain is accepting simultaneously what the two eyes are seeing, it will be able to make them into one picture of the soldier in his box, provided each eye is looking directly at its picture. The patient is said then to have *simultaneous perception*.

Suppression does not, however, affect the whole visual field equally, and the part of the right visual field that would only be seeing a space in its picture may be suppressed while the corresponding part of the left is seeing.

THE MODERN TREATMENT OF SQUINT

By J. L. WILKIE, M.B., F.R.C.S.Ed.

Ophthalmic Surgeon, Newcastle Eye Hospital.

IN the normal state when the gaze is directed upon an object the image of that object falls at the fovea centralis of each retina. Squint is an abnormal condition in which there is loss of this binocular central fixation. It should be noted that it is not a matter of parallelism of gaze. Parallelism can only occur normally when the object looked at is distant, whereas for any nearer object the directions of gaze (visual axes) of the two eyes will cross at the object without the person being accused of squinting. Under normal conditions the degree of convergence varies with the degree of accommodation required to give a sharp image of the object in each eye.

If an individual is hypermetropic he has to employ some of his accommodation power even to see distant objects sharply, and more than the normal amount for other objects. There will therefore be a tendency for convergence to exceed what is needed to direct the eyes simultaneously on the object. Such a tendency can usually be overcome because of the considerable amplitude of vergence possessed by most pairs of eyes. Thus, supposing the eyes are accommodating one dioptré, they can be expected to assume a position converging on an object one metre away. They are able, however, without changing the amount of accommodation, to converge considerably more than this, or to diverge somewhat from it.

The unconscious desire to make both eyes look at the same object depends upon their being able to provide the brain with sufficiently similar pictures for the brain to be able to fuse these into one. Something may occur to interfere with the desire to fuse, for instance, some interference with the production of a satisfactory image of the object in one of the eyes, and the latent tendency to convergent squint becomes manifest. A large proportion of children's squints are of this type, starting about the age of three. It might be thought that, if the cause precipitating the appearance of such a squint is transient, there should be no need to treat the case. In the young child, however, the squint often becomes permanent unless treated.

Consider what the state of affairs is while the child is squinting. He is looking at object O with the straight eye, but the other is directed towards another point P. If the brain accepts both pictures equally and combines them, O and P both occupy the centre of the fused picture, and there is *confusion*. Further, O is seen centrally by the straight eye, and eccentrically by the squinter, so that in the fused picture it is seen twice, and there is *diplopia*. A young child does not complain of diplopia; he often gets over it quickly, if he cannot readily bring his eyes straight, by suppressing what the squinting eye is seeing. He may feel too that he gets a satisfactory picture of what he needs to see more easily by fixing with the one eye rather

retinal correspondence. He will see double, and his reflexes try to restore the *status quo*. This is what occasionally happens after operation for squint when done without regard to the state of binocular vision, although it should be noted that when the false correspondence is not too strong, an operation calculated to correct very fully the physical degree of squint may allow re-establishment of true correspondence and loss of the false. It is obviously wiser, however, to reawaken the true before operation is undertaken. When the attempt to do so is unsuccessful, the outlook in regard to really satisfactory results from any treatment is not good.

It is the aim of the orthoptist to induce her patient to look with the two eyes simultaneously without suppression, but she has to ensure that retinal correspondence is true, otherwise the free gaze by the two eyes bringing similar images on parts of the retinae that ought not to correspond will intensify the false correspondence.

If correspondence is true the patient can be allowed to manipulate the tubes himself to bring each picture into the view of his eye. The axes of the tubes will cross each other at an angle approximately equal to the angle of squint. He is invited to put the soldier into and out of his sentry box, although if suppression is present he may not be able at first to do so. In treatment, repeated movements are used to attract attention by the suppressing eye. Besides moving one picture in relation to the other in this deliberate way he can also make rapid chasing movements. The orthoptist moves one tube with a picture of a butterfly, for instance, and the child moves his tube with a diagram of the net to catch it. The attention required for such rapid alterations of fixation does not allow time for suppression to come into operation.

When suppression has been overcome, it should be possible for the child to see double. Thus, proceeding to the fusion pictures mentioned above, he will see two men, one without a head, and the other without a leg. If he brings the pictures together he will be able to make them into the one complete picture of the man. The object of further training now is to establish this fusion further so that, even when the angle at which the pictures were originally fused is gradually altered, fusion is maintained and the patient re-learns to use his amplitude of vergence.

If there is false correspondence, the patient would want to set the tubes at an angle different from the objective angle of squint when putting the sentry into his box. It is this disparity between the objective and subjective angles of squint that proves the presence of false correspondence. The orthoptist sets the tubes at the objective angle. Small repeated movements are then made with one of the tubes in the direction of increasing the squint. The object is to reawaken the patient's acceptance of binocular vision with true correspondence, and any tendency to move the tubes towards the false angle is rigorously avoided.

All that can be done with exercising is to offer a concentrated stimulus to true binocular vision for a very small part of the time he is using his eyes.

Simultaneous perception pictures are available in graded sizes, and the patient must have at the most very limited areas of suppression to obtain simultaneous perception with the smallest.

A more advanced test is the presentation of pictures that have parts in common but are not entirely similar. A man may be shown without a leg in one and without his head in the other. To see the picture of the complete man at once the patient must have *fusion*.

The most complete binocular vision is *stereoscopic*. In the simplest tests for this the same two objects may be shown in each picture, but one object does not occupy the same horizontal position relative to the other.

The apparatus used for such tests is usually of the amblyoscope type. The necessary features are two angled tubes, a mirror being placed at the angle in each so that the patient's eyes looking through at their ends may see, reflected, pictures placed at the other ends. The tubes are so mounted as to be movable into different positions according to what may be required by those of the eyes. The use of angled tubes with mirrors is needed, as otherwise allowance could not be made for even moderate degrees of convergence. A lens is placed at the eye end of each tube so that each picture is seen as if in the distance. Most instruments used now are not actually the original amblyoscopes but have more adjustments, and are larger and more solidly constructed. For convenience, I am grouping all types as amblyoscopes in this article. The same apparatus is used in treatment.

RETINAL CORRESPONDENCE

Besides suppression, which does not affect the whole visual field, another mechanism may be used unconsciously by the patient. Whether the gaze of each eye is directed at the same object or not, an effort is made to accept the two images of any object as representing that one object and not two. It is not just that when one eye squints the image it offers comes to be recognized as giving a false idea of the direction of various objects in space, but a new correspondence between the two retinæ is produced.

It has already been indicated that normally, varying degrees of convergence are used, and also conjugate movements, to keep the gaze of each eye directed at the same object. Using the idea of retinal correspondence, the maculæ correspond, and the position of one eye relative to the other is maintained in recognition of their correspondence. Such correspondence has to be learnt as the child develops, and although fairly well established by the usual age at which squints occur, it is often still possible for the child then to develop a new false correspondence more in keeping with the squinting position of the eyes.

Once a false correspondence is present it perverts the normal reflex that should keep the eyes straight. It will now tend on the contrary to perpetuate the squint. The effect of physically bringing the eyes straight will be equivalent to making the patient squint physiologically in relation to his

training may have to be deferred because of age. Even when glasses keep the eyes straight it is as well to employ such training, as fusion may be weak, allowing the squint to reappear easily. If glasses merely reduce the angle of squint without completely straightening, it is obvious that suppression and false correspondence will continue to be developed by the patient. Occlusion is necessary; and often operation is deferred until the child can fuse.

Squints that appear *at birth or early infancy* cannot have been brought about by accommodation. Refractive error may be negligible, although it is wise to correct any considerable error with glasses. Paresis of the sixth nerve may have been the original cause. The effect of binocular vision is likely to have been that no opportunity with the eyes straight has ever been afforded the child to develop true retinal correspondence, and there is nothing that orthoptic treatment can reawaken. Probably not many surgeons would care to do it in a child so young, but the only rational treatment would involve very early operation. Even to wait until the child is over a year old would probably be too late for reasonable binocularity to result.

Other cases may arise at any age because of transient paresis or other obstacle to binocular vision allowing the establishment of squint. Treatment of these is likely to be similar to the accommodational cases.

In *divergent squints* help from the correction of refractive error can only be hoped for if the latter is myopia. In most cases, however, refraction is unimportant. Fusion and correspondence are usually quite good and operation is practically always needed.

In a considerable number of cases, fusion cannot be obtained, and in such, operation may be required for cosmetic purposes. It is as well to remember that the patient is not expected to have any strong reflex mechanism for maintaining straightness of the eyes after operation, and some alteration, in the way of increased divergence, may occur even years after.

In children there is a tendency for paretic squint to become concomitant. In adults, binocular relations are well established and the main complaint will be of the diplopia and confusion rather than of the appearance of squint. Some time has to be allowed for any natural recovery that is going to occur in the affected nerve. Even with recovery of the nerve the antagonist of the muscle supplied may have shortened and some squint remain. In such a case operation may be advisable to weaken the antagonist. Attention is paid to effects on other muscles, however, and it may be found more satisfactory to operate on a muscle in the other eye to allow its movements to conform with the affected one rather than *vice versa*.

In paralysis, or severe paresis of muscles, it may still be necessary to be content with avoidance of diplopia by occlusion of one eye.

OPERATIVE TREATMENT

The *rectus muscles* reach their insertions in front of the equator of the eyeball. They are therefore easy of access. In addition, their action appears at once more straightforward than that of the oblique. The medial and lateral recti

The rest of the time, if he is still squinting, he would be re-adopting the false correspondence unless one eye is occluded. Therefore as a practical matter, once true correspondence has been shown to be usable by the patient, it is as well to proceed to operation as soon as possible. Immediately after operation, during the patient's stay in hospital, opportunity can be taken to give orthoptic treatment at least daily, and when he fuses truly, with ease he can be encouraged to keep both eyes open throughout the day. Having made straightness easier of attainment, the patient should then find it natural to use the true correspondence when looking at his surroundings without occlusion.

OBSTACLES TO BINOCULAR VISION

The obstacle that has already been commented on is hypermetropia. It is an obstacle because of its bearing on accommodation and so upon convergence. *Refractive error* may, however, have a further effect by producing inequality of vision in the two eyes. The degree of hypermetropia may be greater or astigmatism more marked in one eye than the other. Such considerations show why one of the first things to do for a case of squint is a refraction test under cycloplegia, and to order glasses if necessary.

Other conditions interfering with the vision of one eye will be noted at the same time, although it may not be possible or expedient to alter them. It will not, for instance, be possible to do anything for a macular coloboma; and it is not worth while needling a cataract in one eye if the other is unaffected. In the latter case images would be too large to fuse with those in the unoperated eye and so allow binocular vision.

Muscular anomalies may be present, making it difficult or impossible to adjust the gaze of one eye to the other. Amplitude of vergence is very much less in the vertical than in the horizontal plane, and if the squint has a vertical component the latter will have to be dealt with early. Among squints of this type, overaction of the inferior oblique muscle, shown by an upshoot of the eye when it looks medially, is a well-recognized indication for operation. Overaction of the superior oblique is much rarer. Not every case of oblique overaction, however, develops a horizontal squint with loss of fusion, as the child may be able to keep the eyes straight when looking ahead. As regards horizontal muscles, indication for operation usually comes later after orthoptic treatment has been carried far enough to ensure fusion, if possible. Some convergent squints, however, may be too marked to allow the amblyoscope to be used easily, so that operation will be needed first to give orthoptics a chance.

TYPES OF CONCOMITANT SQUINT

The most common type of squint is the *accommodational*. This type has already been taken as an example in introducing the ideas underlying orthoptics. The age of onset is commonly about three years, and may be earlier or later. Glasses are ordered at once, and occlusion may be necessary, but orthoptic

OPHTHALMIC EMERGENCIES

By J. W. TUDOR THOMAS, M.D., M.S., D.Sc., F.R.C.S.

Senior Ophthalmic Surgeon, Royal Infirmary, Cardiff.

SOME of the most common ophthalmic emergencies are injuries affecting the eye, which may be of a perforating or non-perforating nature. A careful examination of the eye will usually enable the diagnosis to be made, but it is often necessary to have an X-ray examination performed, especially to determine the presence and position, or the absence, of a foreign body in the eye or orbit.

FOREIGN BODIES IN THE EYE

Small foreign bodies may perforate the eye through the sclera, causing little disturbance and only slight redness and discomfort, and may be in the vitreous quite unsuspected for a time.

Such was the case with a patient who was talking to a neighbour and tapping a hatchet on a low garden wall when something flew up to her eye. It caused so little trouble that she thought it was only a little dust that had gone in to her eye, and it was three months before she sought advice because of some mistiness of vision. A small piece of steel was then discovered in the vitreous, which was successfully removed with the aid of the magnet.

Small foreign bodies in the eye often imbed themselves in the cornea, and may escape attention unless a careful examination is carried out with magnifying glasses or a loupe. It is also necessary to use a large lens of about +13.00 D to focus the light on the cornea, or to use a concentrated beam of light from an electric torch or ophthalmoscope. A meticulous examination should be carried out, particularly if the iris is dark brown in colour, when a foreign body such as a piece of coal dust may be very difficult to see by casual observation.

Method of removal.—When removing such a foreign body it is wise to use magnifying glasses, if required, so as to see clearly that when removing or dislodging the foreign body there shall be no unnecessary trauma to the adjoining corneal epithelium. After removal of the foreign body, a small rusty looking ring may be seen, and this coloured matter should be carefully scraped away in order to allow the little wound to heal quickly. It is hardly necessary to emphasize the need for ensuring that any spud or needle used to remove the foreign body should be sterile.

Following removal of the foreign body, drops of 10 per cent. sodium sulphacetamide may be instilled, and drops of paroline for the purpose of lubrication. Alternatively, some metaphen ointment, 1 in 2500, may be inserted.

If a foreign body is not found on the cornea or in the conjunctival sac or

are the muscles most frequently operated on. The operator may desire either to weaken the action of a muscle, or to strengthen it.

To strengthen action, the muscle tension is increased. In the simple advancement operation, the tendon would be cut from the globe at its insertion and stitched down again farther forward. A pure advancement is limited in its effect by the limitation of space in front of the original insertion, as it is obviously impossible to take the tendon right on to the cornea. It has therefore usually been the practice to pass the stitches through the muscle some distance back from the cut insertion, and to excise tissue anterior to them, except what is necessary to allow the stitches to keep their hold of the muscle. The resection part of the operation has come to assume more importance than the advancement.

To weaken a muscle, relaxation of its tension is aimed at. The most generally used method is suture of the cut tendon to the sclera at such a distance behind the original insertion as has been reckoned suitable for the case. Another method is to stitch the cut end of tendon to its original insertion, but to leave the loop just sufficiently slack to allow the tendon to slip back the appropriate distance.

Of the two *oblique muscles*, the inferior has received more attention. Overaction of the inferior is more common than of the superior, but also, although its insertion is behind the equator, even farther behind than the superior, the muscle itself takes origin near the orbital margin, where it can be approached with reasonable ease and the muscle fibres cut across. It is now customary to remove a portion of the muscle altogether, and the operation is described as *myectomy*. The object here, of course, is just the opposite from resection as described for the recti. The latter, with the aid of stitching, is to increase the tension on muscle fibres and so enhance their action. Rejoining of the cut ends of muscle is not desired in myectomy. A refinement on this operation is the approach through the lower fornix which avoids leaving a visible scar. For this purpose a hook was devised for finding and holding the muscle before the conjunctiva is incised. Lately, more interest is being taken in recession of the insertion of the inferior oblique.

Coming to the superior oblique: in general, surgeons have not found operations on it satisfactory. It has been found best to depend to some extent upon the fibrous attachments to prevent complete loss of action on cutting the tendon of the superior oblique. Suitable approaches from conjunctiva can be made to reach the insertion, and the tendon before it passes under the rectus. The latter part of the tendon has been found the most suitable for *tenotomy* in cases of overaction of the muscle.

CONCLUSION

In the treatment of squint provision of spectacles, occlusion, orthoptic treatment and operation may all be needed. It is particularly important, however, that all should be coordinated under unified supervision.

the lens is accompanied by some degree of lens opacity, but concussion damage to the lens usually takes some time before a traumatic cataract becomes evident. Concussion and other injuries may produce choroidal tears or choroido-retinal damage, or detachment of the retina. It should always be remembered that myopic eyes—particularly if highly myopic—are very liable to detachment of the retina. This may occur spontaneously, but injury, even trivial injury, is often a determining factor in producing the detachment. Consequently, injuries to myopic eyes should be regarded as potentially more serious than might at first appear.

Extensive *wounds of the conjunctiva* require suturing, and wounds of the cornea often require covering with a conjunctival flap after removal of any prolapsed iris tissue. Wounds involving the ciliary body are always serious, and in such cases the possibility of the development of sympathetic ophthalmia later on must be considered.

More extensive injuries, including *fractures of the orbit*, will be appreciated as serious conditions.

Atropine drops are often required in the treatment of injuries of the eye, but unless there is obvious need for the use of atropine it should be used with caution, recognizing that it may precipitate the onset of glaucoma in a person pre-disposed to that condition, particularly if over forty years of age, the danger being rather more if the patient is fifty or sixty years of age, or older. It is not usually necessary to order atropine for a patient with a foreign body on the cornea, or a small corneal laceration involving only the epithelium.

BURNS OF THE EYE

Chemical burns.—When the burns are chemical in nature the eye should be bathed as soon as possible to get rid of the irritant. If the nature of the chemical is known, an appropriate solution is used: 2 per cent. sodium bicarbonate for an acid burn, and vinegar diluted, a tablespoon to a pint of water, for an alkaline burn. Alternatively, 1 per cent. acetic acid may be used, or boracic acid lotion. If these are not available at once, lukewarm saline should be used. In the case of *lime burns* an attempt should be made to remove any small particles of lime, and an appropriate solution for neutralizing would be 2 to 5 per cent. neutral ammonium tartrate. Should the patient be seen at an early stage, water or any non-irritating solution should be used freely to wash out the conjunctival sac as thoroughly as may be possible. If the nature of the chemical is not known, a piece of litmus paper applied to the lids will indicate whether it is acid or alkaline. The proteinates formed from an acid burn are insoluble, but alkaline proteinates are soluble and continue to cause damage after all free alkali has been removed. Consequently, it is important to continue to apply neutralizing acid solutions for some time if the damage is to be kept minimal.

For *accidental burns with tear gas* (chloracetphenone), sodium sulphite

under the upper eyelid, a search should be made for an abrasion of the corneal epithelium. A clue to its presence may be found by observing the reflection of a window on the corneal surface, and is indicated by a localized irregular image. This can be confirmed by the instillation of a drop of 2 per cent. fluorescein, which stains green any area of epithelial abrasion. Should the foreign body be deep in the cornea it is better not to persist in attempts to remove it but to refer the case for treatment to an ophthalmic department.

WOUNDS OF THE EYEBALL

These may range from trivial lacerations of the conjunctiva to obviously serious and extensive damage to the eye as a whole.

Small lacerations of the conjunctiva heal readily, and treatment is directed to the removal of particles of dirt and to keeping the eye free from infection. The condition may be complicated by subconjunctival hæmorrhage, which, although alarming in appearance, clears up readily.

Whether an injury be caused by a sharp object such as a knife, or a blunt object such as a tennis ball, it is necessary to decide whether there is any intra-ocular damage, or whether the injury is likely to have serious consequences. A few observations such as the following will help in coming to a conclusion:—

The cornea or sclera may exhibit signs of laceration. The pupil may be pear-shaped, owing to prolapse of a portion of the iris into a corneal wound. Blood may be seen behind the cornea in the anterior chamber. Even in the presence of a clear cornea and a round pupil, it may be that extensive intra-ocular damage is present, and this may be ascertained by asking the patient what he can see with the eye. Further examination with an ophthalmoscope may reveal hæmorrhages in the retina or the presence of a cloud of blood in the vitreous, obscuring a view of the fundus.

Non-perforating injuries can produce paralysis of the iris with a dilated inactive pupil, or hæmorrhage inside the eye. If light is reflected from a retinoscopy mirror, or from an ophthalmoscope into the eye, normally a good red fundus reflex should be obtained. If, however, the media of the eye are cloudy, this reflex will be much diminished, and if the vitreous is full of blood there is no red reflex and the interior of the eye appears black when viewed in this way.

Iridodialysis, or rupture of part of the iris near its root, may be accompanied by hyphæma—blood in the anterior chamber—and, in addition to seeing the tear in the iris, the pupil can be seen to be flattened on that side.

The lens and the retina.—Both perforating and non-perforating injuries can dislocate the lens of the eye. The dislocation may be partial or complete, and the lens may lie in the vitreous, or in the anterior chamber, or may extrude through a tear in the sclerotic to lie beneath the conjunctiva, where it forms a visible lump although often obscured with blood. Direct injury to

in the course of an attack of iritis, for instance, when the pupil might be small and irregular and fixed by adhesions to the lens.

The diagnostic sign of acute glaucoma is increased tension or hardness of the eye. This may be appreciated by pressure with the tip of a finger of each hand on the eye through the upper eyelid, with the patient looking down. Comparison with the other eye, or with a normal eye, should give an unmistakable impression of increased resistance in the eye with acute glaucoma. In a typical uncomplicated case the pupil will be somewhat oval, immobile and semidilated, and the iris, on close examination with focal illumination, will appear to be nearer to the cornea than the normal (shallow anterior chamber). The eyeball will appear congested and red, and the vision in the eye will be much reduced or even entirely lost. It may be possible to elicit a history of gradual loss of sight in the eye before the acute attack, or of failing vision in dim light, or of increasing restriction of the visual field—indicating a condition of chronic glaucoma complicated by an attack of acute glaucoma. The eye in acute glaucoma is usually less tender to palpation than an eye with acute iritis.

A useful point to elicit in the history is whether the patient has been seeing coloured rings (halos) around the lights for some time, indicating pre-existing chronic glaucoma. Halos may also be seen in the course of acute glaucoma before vision in the eye is unduly diminished. The cornea in acute glaucoma is of a dull or steamy appearance due to œdema caused by the tension of the eye, and this gives the impression of the eye looking dull and lacking in lustre, and imparts a muddy appearance to the iris. Close examination with a loupe will reveal minute raised dots and irregularities in the corneal epithelium, extending over the whole of the cornea and caused by œdema. Should the tension of the eye be raised and the pupil be irregular or small, it suggests acute glaucoma complicating acute or chronic iritis. Should the pupil be very large and the patient elderly, it is worth while thinking of the possibility that the acute attack may have been brought on by the use of atropine drops.

Certain other eye diseases are prone to be complicated by acute glaucoma, such as thrombosis of the central retinal vein, or the presence of an intra-ocular tumour, or dislocation of the lens into the anterior chamber. Acute glaucoma may also arise in injured eyes, perhaps with adhesion of the iris to the cornea, and may be a complication following operations on the eye, such as needling for cataract. In children acute glaucoma often produces vomiting.

Treatment.—The pain of acute glaucoma is very severe and often requires morphine for its control. Eserine drops, $\frac{1}{2}$ per cent., should be instilled into the eye, and attempts made to dehydrate the body by reducing fluid intake and administration of Epsom salts, together with rest in bed and diaphoresis. Hot applications to the eye are of assistance in the relief of pain. Usually operation is required, although not necessarily immediate,

solution may be used: 0.4 per cent. sodium sulphite in glycerin and water. Tear gas is soluble in glycerin and in sodium sulphite solution.

For the relief of pain it is not advisable to use cocaine drops, but if anything is used apart from irrigation, neutralizing agents, and paroline oil, it would be less injurious to use drops of $\frac{1}{2}$ per cent. holocaine or butyn, or an ointment of 1 per cent. butyn or holocaine, or $\frac{1}{4}$ per cent. pontocaine.

If the conjunctiva of the globe appears white and avascular after a burn it indicates a severe injury likely to lead to corneal complications, and calls for operative treatment, such as excision of the damaged conjunctiva, and plastic repair or mucous membrane graft if the loss of tissue is considerable.

When the skin of *the lids* is damaged by burns of the first and second degree, after cleansing with saline and appropriate neutralizing solution, the area should be covered with a layer of tulle-gras, after application of a little penicillin powder or cream. Over the tulle-gras is placed gauze and wool wrung out of normal saline. Third degree burns of the lids require skin-grafting to prevent contraction of tissue and eversion of the lids.

Radiation burns.—Visible light (3,500 to 7,500 A.U.) does not normally produce a burn.

The long infra-red rays (7,500 to 12,000 A.U.) reach the retina and tend to affect the retina, lens and iris, usually after prolonged exposure, but acutely after direct observation of the sun (eclipse blindness).

Ultra-violet light (below 3,000 A.U.) is abiotically active and produces burns. Intermittent exposures produce a summation effect unless there is about twenty-four hours' interval for repair to take place. There is usually a latent period of six to eight hours before photophthalmia and conjunctivitis appear, the effect being produced by epithelial nuclear fragmentation and the breaking down of swollen epithelial cells, and nerve endings in the cornea are exposed. The effects are quite superficial but cause much pain and acute discomfort, so that the patient comes to be seen as an ophthalmic emergency. Treatment with saline lotion, paroline drops, or 10 per cent. albucid drops, is usually sufficient, together with rest for the eyes and dark glasses.

GLAUCOMA

The chronic form of glaucoma, glaucoma simplex, is insidious and gradual in its development, without pain and producing a gradually contracting visual field. Acute glaucoma, however, develops suddenly with much pain in the eye and hemicrania, and with redness of the eye. An acutely painful red eye without history of injury suggests glaucoma, acute iritis, or perhaps acute conjunctivitis.

Although an eye with *acute glaucoma* usually presents certain signs, such as a semidilated inactive pupil, often somewhat oval in shape, it cannot be stated that these signs are always present, because acute glaucoma may arise

THE CARE OF THE SCALP AND HAIR

BY GEOFFREY HODGSON, M.B.E., D.M.

Dermatologist, United Cardiff Hospitals; Lecturer in Dermatology, Welsh National School of Medicine.

ONE of the oldest of recorded medical prescriptions was for baldness, and was prepared for Ses, mother of Teta, the king of Upper and Lower Egypt some 5000 years ago. An invocation was spoken to the sun over a large pill of iron, red lead, alabaster, onions and honey (Pusey, 1933).

Although the dignity of man be enhanced by grey hairs and a shining pate, most people attach greater importance to the preservation of their hair. They do not, however, go to such lengths as the old ladies of Drumconrath in Ireland. They believed so fervently in the scriptures where it was written that all the hairs of their heads were numbered, that they carefully stored them all away in the thatched roof of their cottage in case they had to account for them at the Last Judgment! (Radford, 1947).

It is considered that a scalp hair has a life of two to four years. The old hairs die and are pushed out by the new hairs forming in the follicles behind them; the new hairs appearing on the surface some six to ten weeks later. In this way, there is a continual loss and regrowth of hair.

GENERAL SCALP AND HAIR HYGIENE

Proper care of the scalp will maintain the normal circulation and the health and regrowth of hair. Progressive combing of strands will prevent the hairs being dragged out by the roots. When the hair is fragile, thin and long, a brush with flexible bristles set in a rubber sponge base is preferable to a comb. Similar brushes with thick nylon bristles are called comb-brushes and are used when the hair is thick and difficult to comb.

Hair brushing is carried out firmly from the nape of the forehead and temples upwards to the vertex. Care should be exercised in women with the itching lozenge-shaped plaque of neurodermatitis (*Lichen simplex chronicus* of Vidal) on the nape, as brushing may cause aggravation.

Hats must be ventilated and fit well; a ring of constriction around the head interferes with the circulation, and increases sweating. It is not good for hair growth to expose the scalp to hot sun. Curling grips and papers may damage the hair shafts. Combs and brushes are personal articles and require washing when the scalp is shampooed.

The *frequency of shampooing* depends upon the greasiness of the hair and the environment; once a week is adequate for the average head. A good white soap may be sufficient, but shampoos can be more satisfactory. There are spirit, soap, dry, and soapless shampoos. Spirit shampoos are employed for

especially if the attack is very recent, when a short delay is justifiable to try to reduce the tension of the eye before operating. Much delay should be avoided unless vision is returning; acute glaucoma can destroy vision permanently if not relieved in the course of three weeks. The length of time may be considerably less if the eye is already very defective due to chronic glaucoma.

ACUTE OCULAR PAIN

Acute ocular pain may be associated with some visible cause, such as a foreign body or injury, acute iritis or acute glaucoma. It can also be due to trigeminal neuralgia or the early stages of herpes zoster. In the course of treatment of a corneal ulcer, acute pain may arise from perforation of the ulcer. Sometimes acute discomfort is due to spasm of the orbicularis causing entropion of the lower lid, especially in old people, and perhaps complicating conjunctivitis. Ocular pain may also be referred in type or brought on by psychological causes.

SUDDEN LOSS OF SIGHT

Fairly complete loss of sight in one eye and very abrupt in onset can be caused by an *embolism* affecting the central retinal artery, and in elderly people there may be changes in the retinal artery leading to thrombosis. Thrombosis of the central retinal vein is not of such sudden onset, and the loss of vision may be confined to one quadrant of the visual field. Acute *retrobulbar neuritis* also can produce fairly rapid loss of sight in one eye.

A condition which is alarming to the patient and which can develop suddenly, is the appearance of a *hæmorrhage at the macula*, blotting out central vision; this may be accompanied by generalized vascular disease and other pathological conditions of the retina. It may also be brought on by injury. Sudden hæmorrhage into the vitreous may complicate choroiditis or vascular disease of the retina, and may occur as recurrent spontaneous hæmorrhages in young people (Eales's disease).

Detachment of the retina, causing the appearance of a curtain coming down over the sight, and restricting vision partially or fairly completely, may be suspected, especially in high myopes. The exact diagnosis of the cause of sudden loss of sight necessitates the use of the ophthalmoscope so that the exact state of the fundus can be appreciated and vitreous opacities or detached retina can be directly observed.

CONCLUSION

There are other eye conditions of fairly sudden onset that may appear as ophthalmic emergencies, such as diplopia due to paresis of ocular muscles, or sudden onset of conjunctivitis due to allergic predisposition, but in the main, emergency conditions are due to injuries, burns, acute glaucoma, acute pain, or sudden loss of sight.

hennas may cause contact dermatitis of the scalp, neck, forehead and ears. A patch test must be applied to the neck for twenty-four hours before the actual dyeing. Hair needs a complete re-dye some three times a year and frequent touching up. Preliminary degreasing of the hair may cause brittleness. Dyeing is safe in young persons with prematurely white or grey hair, if precautions are taken, but is not advised in the older patient.

Dystrophic hair, extensive psoriasis, septic lesions of the scalp, and seborrhœic dermatitis are *contraindications*. Dermatitis may be mistaken for a weeping seborrhœic dermatitis and the dye may also activate a quiescent seborrhœa. If dermatitis has occurred, the hair is washed with soap and water to remove excess dye and hydrogen peroxide, or 25 per cent. sodium thiosulphate compresses are used. Ordinary washing is then carried out, and the dermatitis is treated on routine lines.

PERMANENT WAVING

Practitioners are sometimes asked if permanent waving is advisable, or detrimental to a scalp condition. Two main techniques exist, which depend for their efficacy upon softening the hair shaft. In the ordinary method, the keratin is softened with an alkali and steamed, the hair being wound round curlers. The "cold wave" employs thioglycollic acid and is a constituent of the preparations advertised for use at home. Thermal burns and discoloration of the forehead, especially in grey-haired persons, may occur from the heat or the alkali, but the dangers of the "cold wave" are contact dermatitis, brittleness and fracture of the hair shafts or damage to the liver by absorption. The incidence of dermatitis of the hands in hairdressers from the technique is high.

Permanent waving of the ordinary type is recommended when a patient has to wash her hair frequently. Scalp diseases, such as oily seborrhœa, psoriasis, ichthyosis, alopecia areata (often erroneously thought to be burns from waving) and lupus erythematosus, are not contraindications. Those with sensitive skins, eczema, or a history of recent seborrhœic or contact dermatitis should be advised against the "cold wave" process and instructed to wear rubber gloves to protect the hands when applying the chemical. A twenty-four hour patch test must be made first to exclude sensitivity. It might be prudent to discourage its use in those with a recent history of jaundice or liver disease.

DYSTROPHIC, DRY, GREASY AND GREY STATES OF THE HAIR

The hair is not a dead structure, and is therefore influenced by physiological and pathological changes affecting the organism as a whole. Sulphur is essential for growth and for vital enzymic oxidation processes. The keratin of the hair and skin acts as a storehouse for sulphur. Hence in infections, intoxications, and dietary deficiencies the dystrophic changes in the hair

greasy hair or with excessive dandruff. Soap spirit B.P.C., containing 65 per cent. w/v of soft soap in industrial spirit, has replaced Hebra's soap. Soap shampoos will serve the average scalp; they consist of soap powders or liquid mixtures of oil (almond, coco-nut), alkali and water. Dry shampoos are not usually efficient and are composed of an alkali and an inert powder which is applied to the scalp and then brushed out. They are sometimes used by women with very long hair, when frequent washing is a burden. Soapless shampoos are efficient for general use, and in brittle or dry states of the hair when a degreasing action should be avoided. They contain modern detergents, such as the sulphonated oils.

Salt water should be rinsed out of the hair after bathing. The routine use of water to dress the hair is undesirable, and may promote a brittle state. A glossy appearance may be imparted to lifeless looking or dystrophic hair, by combing the white of an egg into the hair occasionally. Some prefer to mix the white and the yolk of the egg with soft soap in a lather and to use this as a shampoo to be followed by a rinse in water.

HAIR DYES

Women with seborrhœa, dandruff or scalp conditions are advised to adopt one of the modern short-cut, close to the head hair styles to facilitate frequent washing and treatment. There is no evidence that cutting or shaving will increase the rate of hair growth; there being a definite length to which the hair grows anyhow. Experiments by Dr. Agnes Saville (1944) suggest that singeing, which is practised to "scal up the ends", may be harmful and by drying the hair far above the singed end may destroy much of the shaft.

Most hair creams and pomades are harmless medically, but the possibility of dermatitis from perfumes and the occurrence of acneiform eruptions with blackheads on the forehead should be remembered, especially in greasy skins from the use of oily scalp creams and vaselines.

Hair dyes.—Patients may ask advice on hair dyeing. Hydrogen peroxide and ammonia used to bleach the hair may cause brittleness and are not recommended in dry dystrophic hair. The vegetable dyes, camomile, henna, and walnut, are on the whole safe and may be used, except in older grey-haired patients, when the prolonged application needed to dye the hair may produce undesired reddish coloration in unskilled hands. In preparing these, the powdered leaves of henna are infused in boiling water, whilst $\frac{1}{2}$ an ounce (14.2 ml.) of camomile flowers are stewed in about a pint of boiling water for 30 minutes and later poured over the hair. The former is used in dark-haired persons, producing a coppery tint, and the latter mainly in fair persons, the tint in brunettes being auburn. Patients with premature grey hairs may wish to use these.

If the hair colour is to be completely changed, paraphenylene-diamine or pyrogallol must be used. Both these "para" group of dyes and synthetic

seborrhœic and pyogenic organisms. Fluid retention in the tissues may be increased by carbohydrates and fats, increasing seborrhœa, whilst protein eliminates the tissue fluid and lessens seborrhœa (Barber, 1948).

Thyroid is given in *the obese flabby person*. It is wise to restrict fatty and greasy foods, chocolate, pig-flesh and milk drinking, but if the patient is of thin disposition further restrictions may aggravate. Here the nervous control of secretion may be a more important factor. Further restrictions are required in the obese, and include ice creams, butter, oils, pastries, cakes, starchy puddings, potatoes, nuts, sugar, sweets and syrups, and jams with much sugar. Protein is increased by meat, fish, fowl, eggs, whole-grain cereals, soups and meat drinks. Salt is restricted, and fresh fruit and green vegetables and salads advised.

When the nervous control of sebaceous secretion is important, as in fatigue states from work or anxiety, small doses of phenobarbitone and belladonna are employed and the exhaustion treated by rest, relaxation, and sleep, with adaptation to difficulties in home or business life. The vitamin B complex and liver preparations by mouth may be administered.

Frequent shampoos are needed with a spirit shampoo, and sodium bicarbonate may be added to the water to aid degreasing. A short hair style is indicated and the hair is best brushed in the morning. Eau de Cologne or bay rum is rubbed into the scalp after exercise. A spirit scalp lotion is used daily, such as salicylic acid and mercuric chloride lotion N.F., but with alopecia, tar and resorcin are added to the prescription:—

Mercury perchloride	$\frac{1}{2}$ grain (32 mg.)
Salicylic acid	8 grains (0.52 g.)
Castor oil	5 minims (0.3 ml.)
Acetone	60 minims (3.6 ml.)
Industrial methylated spirit	to 1 ounce (28.4 ml.)

For gross oiliness a few drops of carbon bisulphide may be applied on cotton-wool; care is taken that the vapour be not inhaled.

Greying of the hair is a normal change of age, and the loss starts at the hair roots, usually on the temples. Premature greying occurs in some families, and sudden greying from shock has been described. Neglect of scalp hygiene and excessive dryness of the hair may predispose to greyness. There is no supporting clinical evidence for the treatment of grey hair with para-aminobenzoic acid and pantothenic acid, which will experimentally repigment the fur of rats deprived of these substances (Ansbacher, 1941). Nevertheless, para-aminobenzoic acid, 500 milligrammes daily, is sometimes prescribed empirically with the vitamin B complex. Thyroid may be tried.

PREMATURE BALDNESS AND PITYRIASIS CAPITIS (DANDRUFF)

The most common cause of *premature baldness* is seborrhœa. The full cause

show that the more vital organs are being supplied at the expense of the hair, nails and skin.

Dry, brittle, and lustreless hair with thinning may be evidence of a low state of bodily or mental health, or may result from neglect of scalp hygiene.

Falling of the hair may occur about 90 days after an acute fever. An old custom was to cut the hair of typhoid patients to prevent such loss and to shorten the illness. Pregnancy, miscarriages, the menopause, anæmias, cachexia, thyroid disease and states of fatigue from illness and continued physical and mental strain and anxiety are common causes. Seborrhœa and dandruff may be present. Syphilis is excluded by feeling the neck glands as a routine in alopecia patients, by the other signs and symptoms, and by the positive serum reaction, which should always be done in acute hair fall, especially in women.

Treatment

Treatment considers the constitutional background, whilst measures to increase the scalp circulation and hair regrowth by brushing, massage (see p. 219), ultra-violet light and diet are instituted. Injections of crude liver extracts have their advocates.

Diet requires food rich in iron, sulphur and calcium. The following are recommended: spinach, carrots, dandelion leaves, broccoli, turnip tops, unpeeled cucumber, pineapples, prunes, onions, raisins, cauliflower, figs, eggs, oatmeal, and fish oils. Adequate protein with fish, meat, cheese, dried milks, soups and meat drinks is indicated, with full doses of iron and vitamin B complex.

Castor and olive oil, nivea cream, or hydrous ointment B.P. can be massaged into the scalp before using a soapless shampoo and the hair should be allowed to dry slowly in front of a fire, as vigorous rubbing in the wet state may break the hair shafts. A strongly alkaline soap is not suitable, but a tar soap may be used if dandruff is present. Shampooing once in ten to fourteen days is sufficient. Women may spray on a light brilliantine.

Excessively greasy hair is part of the seborrhœic state. It may occur on its own as seborrhœa oleosa in adolescence, but may also be associated with acne, pityriasis capitis, and seborrhœic dermatitis. Hair fall may be rapid and serious, requiring urgent treatment. Factors that augment the seborrhœic state will likewise increase the greasy state of the scalp. These are endocrine, dietary, metabolic and fatigue states from physical work and nervous tension. The vitamin B complex may have some influence on seborrhœa. Cachexia, as in tuberculosis, may increase the seborrhœa.

The endocrine influence may be related to the androgen-œstrogen ratio, with excess male hormone from the adrenals or gonads increasing seborrhœa in opposition to the œstrogens, first in action at puberty. Some women develop greasy hair at the menstrual period. Diet may influence the secretion of fatty acids and subsequent skin sterilization, allowing infection by

th matted grease or scales an olive oil compress is applied or cold cream is spread into the areas and washed off in the morning. A modern detergent, such as cetavlon, 2 to 5 per cent., may be used to clean the scalp. Treatment is gentle in the early stages as the scalp may easily be inflamed. Scalp lotions are applied with the finger tips, on cotton-wool pledgets, with a medicine dropper or with an old tooth brush, along a series of hair partings. The following scalp lotion will control the average case of pityriasis capitis, the tar being included in a case of hair loss:—

Solution of coal tar	30 minims (1.8 ml.)
Resorcin (or chloral hydrate)	10 grains (0.65 g.)
Perchloride of mercury	1 grain (65 mg.)
Industrial methylated spirit	120 minims (7.2 ml.)
Castor oil	5 minims (0.3 ml.)
Water	to 1 ounce (28.4 ml.)
Lavender oil in sufficient quantity.	

In fair-haired people chloral hydrate, 10 grains (0.65 g.), should be used instead of resorcin, which may stain the hair. In women, a spirit lotion may cause the hair to become too lank, and to offset this, 30 to 40 minims (1.8 to 2.4 ml. — 6-8 per cent.) of glycerin are added, with a few drops of almond oil. For men the castor oil is increased to meet the individual case.

Should there be an excessive amount of dandruff or early seborrhœic dermatitis it will be necessary to use, in addition to the daily lotion, a vanishing-cream sulphur preparation once or twice a week, or an oil for a very dry scalp. It is convenient to use this the night before the scalp is shampooed:—

Precipitated sulphur	10 grains (0.65 g.)
Salicylic acid	10 grains (0.65 g.)
Lanette wax	20 grains (1.3 g.)
Liquid paraffin	120 minims (7.2 ml.)
Water	to 1 ounce (28.4 ml.)

In male-type baldness occurring at the climacteric or associated with ovarian dysfunction, local application of œstrogens, diœstrol ointment B.D.H. (2.5 per cent.), may be given a limited trial, but absorption may give rise to menstrual bleeding or painful swelling of the breasts.

Pediculosis of the scalp may be mistaken for pityriasis capitis. The "nits", however, may be found attached to the hairs and cannot easily be detached as with dandruff scales. Treatment is easily given with lethane oil 384 special. The hair is parted at one-inch intervals and not more than 60 to 120 minims (3.6 to 7.2 ml.) is applied on cotton-wool. The scalp is not washed for a week, and the dead nits are then combed and shampooed out. The lethane is applied for a further week.

MESSAGE AND LIGHT TREATMENT

Routine *scalp massage* can be practised at home by patients with dystrophic

of baldness in men is not understood, but evidence suggests the important action of androgens. Eunuchs do not go bald and castrated men tend to keep their hair (such surgical advice, however, might not commend itself to patients with premature baldness!). An inherited family tendency is often present, and the androgens may thus produce the baldness in someone genetically predisposed. Seborrhœa oleosa may be associated, or the hair may be dry and brittle, the scalp being covered with dry branny scales of dandruff which fall like a shower on to the shoulders. The hair may be plastered down on a greasy scalp. The mere presence of dandruff, however, may not cause any hair loss, other factors such as the genetic-androgen background being required as well.

The hair loss starts in the early twenties or thirties. A classical "M"-shaped anterior hair line appears as the hair recedes from the temples and vertex. Hair fall may be rapid, being seen on the pillow at night or on the comb.

Dandruff is caused by infection of the scalp with a yeast-like organism called the *Pityrosporon* of Malassez. The scalp has to be in the seborrhœic state in order that the organism should thrive and produce pityriasis capitis or frank seborrhœic dermatitis. Some women may develop excessive dandruff at the menstrual period and after parturition; the seborrhœic manifestations having been quiescent in the later months of pregnancy. A similar change in the androgen-œstrogen ratio may account for the sudden development of seborrhœa with excessive dandruff formation in some women at the menopause, and also for the male-type of baldness sometimes associated with ovarian dysfunction and the climacteric. Dandruff will often affect women who do not like to wash their hair too often because of some hair style, or because of an erroneous belief that the scales are a sign of a dry scalp and washing will only make it drier. Treatment of dandruff is required in the efficient management of acne.

Immediate treatment is needed when there exists a family tendency to premature baldness. In oily seborrhœa, the hair loss may be alarming and the prognosis is guarded. In premature baldness with dandruff and a good family history the need for constant treatment is emphasized, and the patient informed that the condition is controllable but liable to recur if neglected.

Patients should be warned that the "dead" hair will continue to fall for some time but at a diminishing rate, otherwise the fall may be attributed to the treatment. Dandruff is infectious and the combs and brushes should be washed often; a mother is advised to wear a linen cap whilst nursing to prevent the scales falling on to the child. The relative importance of the background factors influencing the seborrhœic state suggest the lines of general medical treatment. Firm hair brushing, combing and massage will loosen the adherent scales. Shampooing nightly is advised in a neglected case, with less frequency as the scalp improves. Should the scalp be covered

HIGH HEELS AND LOW HEELS

By NORMAN C. LAKE, M.D., M.S., D.Sc., F.R.C.S.

Senior Surgeon, Charing Cross Hospital.

THE outstanding feature of what is called fashion is that it is subject to quite rapid change and yet, if judgment can be based on recent advance information in the daily press, the high heel seems destined to remain and even to become higher still. High heels evidently die hard. They have a long history behind them, having been introduced in ancient Egypt, although their more recent revival dates from Catherine de Medici in the sixteenth century.

Undoubtedly the primary reason for the adoption of a heel was a utilitarian one. The heel is the portion of the footwear which comes in for most of the wear and tear, and in order to overcome this, extra thicknesses were added for economy's sake. The high heel, on the contrary, was introduced to enhance the height of the wearer and later there was added to this a decorative effect. The Italian "chopine", literally a shoe on stilts, represented another attempt to increase the apparent height of the wearer, but it was rather short lived. The modern "platform" shoe with its raised sole is, however, a mild return to the idea of the chopine, the development of which will be watched with interest. That high heels are limited to feminine wear is the best indication that the main factor in their popularity nowadays is fashion and smartness. It will be agreed that all criteria of fashion, smartness and beauty are relative and transitory, but at present the high heel is apparently attractive to the great majority of women. The tapering effect such heels produce tends to camouflage the shape and size of feet which in themselves are often no ornament, whilst the height of the wearer is not only actually enhanced but a deceptive appearance of further height is also gained. Apart from fashion for fashion's sake (and women readily conform to the herd instinct in this respect), these are probably the main reasons which influence the choice of high heels. Anyhow, the high heel is still with us and looks like remaining for some time, despite all its anatomical and physiological drawbacks.

EFFECT OF HIGH HEELS ON POSTURE

One has only to watch the rather mincing gait which some women adopt when wearing really high heels to see that the length of the normal stride is thereby reduced. The reasons for this are much more involved than would appear on cursory examination and need not be discussed here. A direct consequence is that full extension at the knee is also restricted; indeed heightening of the heel is one of the methods adopted when it is desired to prevent full knee extension in some internal derangements. In

hair or scalp diseases with much scaling, as in psoriasis, pityriasis capitis, premature baldness, early seborrhœic dermatitis, or ichthyosis. Exercises consist of placing the separated fingers on either side of the scalp and firmly rotating the scalp on the skull beneath. The vertex is gradually approached from the occiput and temples. The scalp may next be forced into a series of ridges which are squeezed together and rubbed one side against the other. Such movements should be made vigorously, causing the scalp to tingle. After the hair has been brushed, the bristles may be pressed firmly into the scalp or the scalp gently struck with them also to cause some stinging of the areas so treated. Opinions vary as to the efficacy of vibrating or high frequency machines with glass applicators, often marketed for use at home, but even if the counter-irritation be negligible the visual effect of a shower of sparks on to the scalp should not fail to impress the most hardened sceptical patient!

Ultra-violet light from a reliable instrument is most useful in the treatment of alopecias and in the scalp conditions here considered associated with constitutional disease or fatigue states. General light baths should be given as well as local treatment. Very mild exposures are first given in fair or red-haired persons or when the hair is sparse. Dark glasses are worn, and the neck and forehead screened with black cloth or paper. It is wise to have some expert guidance before starting home treatment. The skin tolerance may be treated by exposing small areas of the bared arm to the lamp for varying times. The usual routine treatment is to start with a duration of one to two minutes at two feet and to gradually increase the time while reducing the distance; a mild sun-burn effect being aimed at, two to three times a week. A rest is required after some weeks as the skin develops a tolerance. Radiant heat lamps have little place in the care of the hair except in septic conditions of the scalp. They tend to cause dryness of the hair.

References

- Ansbacher, S. (1941): *Science*, 93, 164.
Barber, H. W. (1948): in MacKenna's "Modern Trends in Dermatology", London, p. 129.
Pusey, W. A. (1933): "The History of Dermatology", Baltimore, p. 13.
Radford, E., and Radford, M. A. (1947): "Encyclopædia of Superstitions", London, p. 140.
Saville, A. (1944): "The Hair and the Scalp", 3rd edition, London, p. 47.

weight to the front and back of the foot. If the foot were a flat board swinging on an axis at ground level this statement would be theoretically and mechanically correct, although even then other factors, such as friction, would affect the issue. As the diagram (fig. 2) shows, the axis of rotation of the

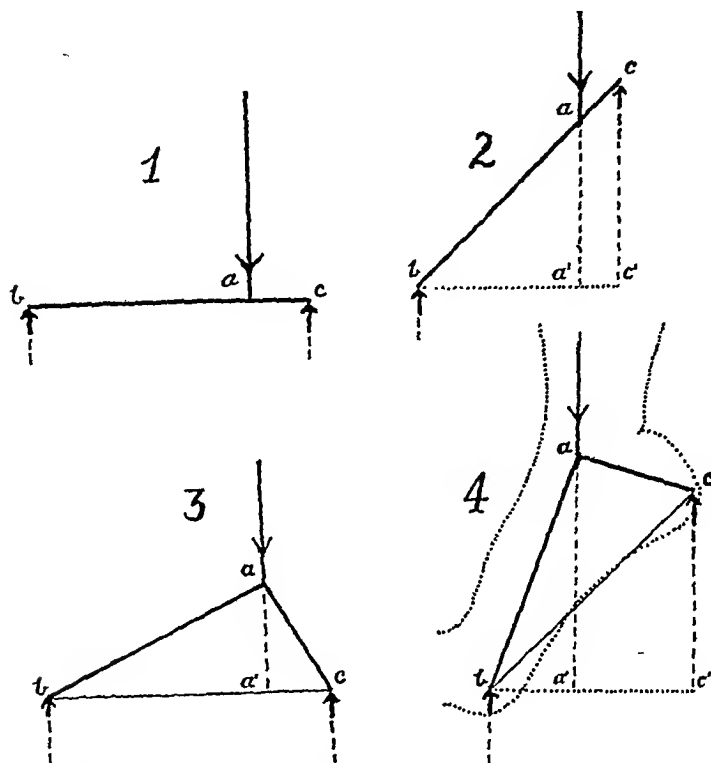


FIG. 2.—Diagrams to illustrate the mechanics of the high heel. If the foot were a simple lever (1) its elevation would produce no change in the proportion of the weight falling on b and c, for (2) ba and ba' diminish in the same degree as ac and a'c'. The actual arrangement is, however, seen in (3) where the relative lengths were obtained from skiagrams. The axis of rotation is at some two inches above the sole, and when the heel is raised the result is seen in (4), where ba' is much diminished whilst a'c' is increased so that a greater portion of the weight is now carried at b.

foot on the leg actually lies at a point about two inches above the sole. Therefore as the heel swings upwards the anterior limb of the lever decreases more rapidly than the posterior, which means that an increasing proportion of the body weight falls on the anterior half of the foot. Mechanically the foot forms a triangle which rotates about its apex. The diagram (fig. 2) illustrates this and figures 3 and 4 give the actual measurements taken from skiagrams.

With the foot flat on the ground the proportions of the arms of the lever are as 1 to $3\frac{1}{2}$; in a high heel the proportion becomes 3 to 4. Assuming a

the upright position the tibia is held tilted a little forwards and the femur slightly flexed on the trunk. It must, however, be confessed that in many women the ankle joint allows a sufficient range of plantar flexion to enable

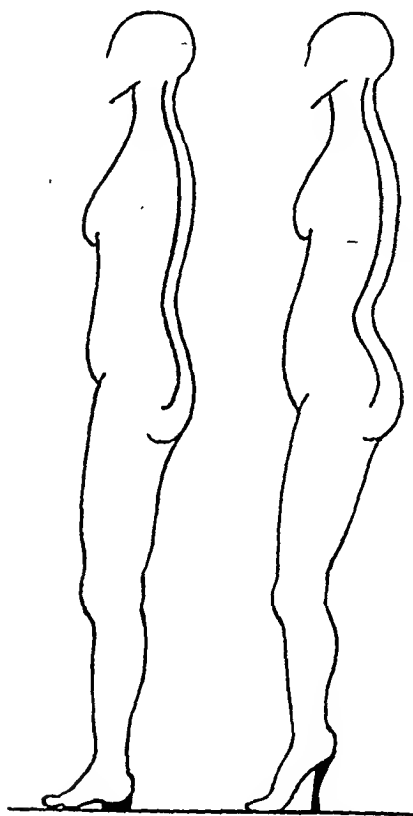


FIG. 1.—Diagram indicating the change of stance which very high heels tend to produce. It should be noted, however, that in many women full compensation occurs by extension of the ankle joint, and the structures above are unaffected.

the tibia to stand upright, compensation for the extension of the foot is limited to the ankle joint, and the skeletal structures above are little affected by the change. Nevertheless, as the heel is raised the centre of gravity of the body is displaced forwards, to counterbalance which the lumbar spine is slightly extended, thus producing a mild lordosis (fig. 1). It would be a mistake, however, to regard these distant effects too seriously, for the human body is so accommodative that even prolonged adoption of this attitude does not seem to cause much trouble in the pelvis or the spine. I cannot therefore agree with those who would attribute the majority of pelvic and lower back pains to the wearing of high heels, although occasionally those with poor adaptation or less sturdy frames may suffer. It is then, upon the feet themselves that the main effects of high heels fall and the results are chiefly mechanical.

EFFECTS OF HIGH HEELS ON THE FEET

A glance at the skeletal basis of the human foot immediately suggests that the massive bones of the posterior tarsus are designed to take the major stresses and strains falling on the feet during either locomotion or standing. The delicately fashioned bones of the anterior half of the foot are obviously more suited to the maintenance of balance and for the "take off". It would seem axiomatic therefore that any pose which throws more strain upon the forepart of the foot, while relieving the heel and the posterior half of the foot of their proper function, is essentially unnatural, using that term in its strict sense, and liable in the long run to produce anatomical and physiological changes of an undesirable character.

Distribution of weight.—It has been argued in the past that the angle of the foot on the leg makes no difference to the proportionate distribution of

It is therefore these articulations, especially the larger mesial ones, which have to bear the brunt of the unwonted stresses. Small wonder that many of the later unfortunate consequences of wearing high heels are to be found in this region. I say "later consequences" because the foot is a long-suffering structure which stands up remarkably well to abuse and which, as every orthopædic surgeon discovers when he tries to correct deformities, requires prolonged and forcible measures to change its configuration. Yet over the years high heels do produce distortion, sooner in some individuals than in others, depending upon the sturdiness of their build, so that the patient has often reached middle age before being compelled to seek relief. The still plastic foot of the teenager is, however, more easily distorted and it is at this age, when young women first take to high heels, that the chief harm

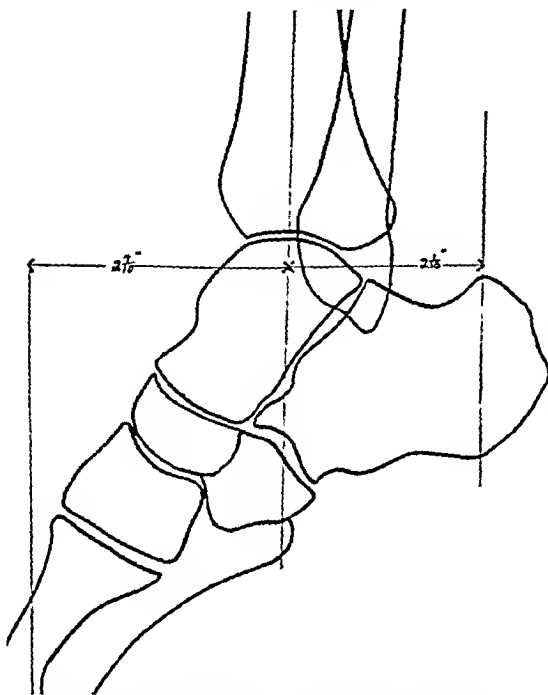


FIG. 4.—Another skiagraphic tracing of the same foot in a high-heeled shoe. The horizontal lengths of the limbs of the lever are marked for comparison with those of the previous tracing. A much greater proportion of the weight now falls on the anterior limb of the lever, i.e., on the metatarsals.

is initiated. Often when older patients seek treatment the damage done cannot be remedied; the calf muscles have undergone secondary shortening, the foot is unduly arched, there are callosities under the metatarsal heads, clawed toes and so on; furthermore the foot is so "set" that it is well-nigh impossible for the patient to walk in a lower heel.

is initiated. Often when older patients seek treatment the damage done cannot be remedied; the calf muscles have undergone secondary shortening, the foot is unduly arched, there are callosities under the metatarsal heads, clawed toes and so on; furthermore the foot is so "set" that it is well-nigh impossible for the patient to walk in a lower heel.

DEFORMITIES OF THE TOES

I have shown that the longitudinal stresses passing down the metatarsals in the high heel position are transmitted to the ground through the heads of these bones, the toes in front carrying little of the weight. The effects of this are many and to a large extent depend upon the relative prominence (that is, projection forwards) of the metatarsal heads. The curve which the metatarsal heads make varies tremendously from foot to foot; sometimes

toes, which it will be readily admitted is almost invariably found in this type of foot. The mere form of the high-heeled shoe, i.e., the necessary angulation at the junction of sole and instep, obviously determines some degree of dorsiflexion of the proximal phalanx, but a further factor of much greater importance, which seems to have escaped notice, is the displacement of the well-developed fibro-fatty pads (which nature provides under the metatarsal heads as under other pressure points, e.g., the heel) forwards under the digits (fig. 5). These masses of fat appear to be rolled forwards by the metatarsal heads much as dough is heaped up in front of the advancing rolling pin. In this connexion it must be remembered that whereas the 1st metatarsal is provided with a special joint on its plantar aspect where it articulates with the sesamoids, the other metatarsal heads have no such provision. As the metatarsals rise to the "take-off" position therefore the 1st metatarsal undergoes a movement of pure rotation about its head as an axis, but the others have to roll forwards so that there is an actual movement of the whole head forwards. It is this, in my opinion, that is responsible for the heaping-up of the fibro-fatty tissues in front of the heads, especially of the 2nd and 3rd metatarsals.

Examination of these feet will reveal the toes with their distal phalanges flexed over a thick roll of fat lying under the proximal phalanges, whilst the heads of the metatarsals are unduly exposed and easily palpated through the thinned overlying tissues of the sole, even although callosities are present. Lacking their normal padding the heads become sensitive to pressure and it is not surprising that patients so often say that they feel as if walking on bare bones.

SOME MINOR DISABILITIES

Secondary to the clawing, other minor painful conditions occur on the toes, such as subungual corns, end pressure on, and deformities of, the nails, dorsal corns, and bursæ over the prominent interphalangeal joints, and so on.

There are other sequelæ to the wearing of high heels, of less importance, but deserving of mention. The rim of the shoe presses unduly upon the tissues over the lower end of the tendo Achilles and there produces a callosity and sometimes a small bursa. Similarly, when a Court or strapped shoe is worn, pressure occurs anteriorly at the edge of the shoe or the strap, especially over the prominent tendon of the extensor longus hallucis, again with the production of corns or callosities.

High-heeled shoes always have a very small area of contact of heel with ground and this conduces to instability with a tendency to "turn" the ankle, a common cause of many a sprained ankle.

PALLIATIVE MEASURES

This recital of the consequences of wearing high heels is formidable enough, and there can be little doubt that there is nothing to be said medically in favour of such a fashion. It is a pity that the public cannot be induced to

the first, at others the second, and rarely the third is the most prominent head and therefore has to sustain the main portion of the stress. This question is further complicated by the fact that at an early stage the forces

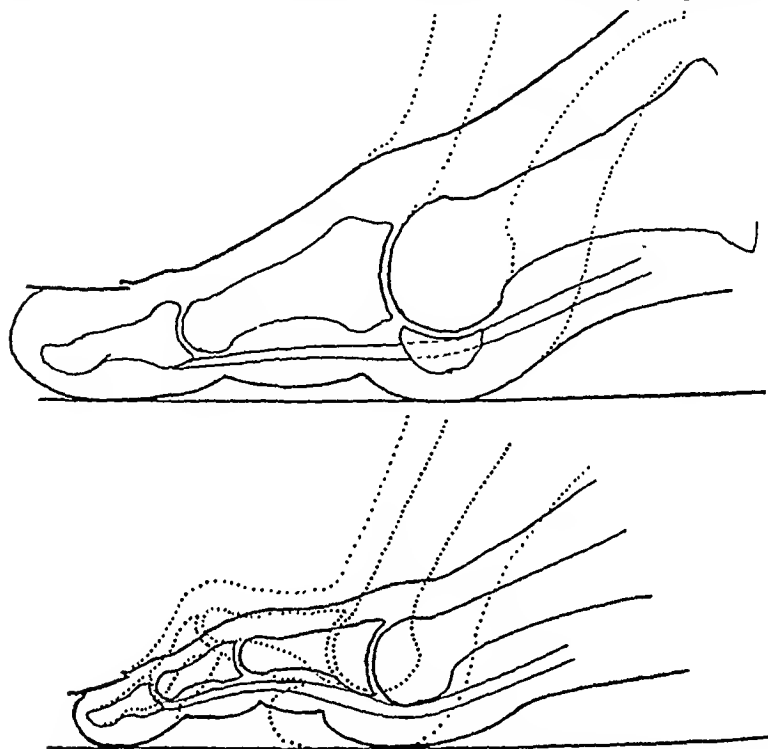


FIG. 5a and b.—Diagrams to illustrate the rolling movements of the heads of the metatarsals. The interrupted lines show the position assumed at the take-off.
 The upper drawing represents the great toe and the lower one the outer toes. The forward rolling of the heads in the latter case leads to displacement of the fibro-fatty pad under the proximal phalanx, which it elevates, whilst the other phalanges are flexed over it.

produce some "splaying" of the foot. In particular the angle between the 1st and 2nd metatarsals increases, the first now deviating mesially. This throws it out of the functional axis of the foot and so, whatever their length and prominence, the second or second and third metatarsals now have to take the main strain. The deviation of the first metatarsal sets the stage for the development of a *hallux valgus*, in the etiology of which high heels thus play an important part, and especially, as I have shown elsewhere (*Brit. med. J.*, 1942, i, 31), if the foot is inherently weak when considered from an evolutionary point of view. The more immediate effect of these changes is to produce painful callosities under the 2nd or 2nd and 3rd metatarsal heads. These will be found in almost every woman who has worn high heels for any length of time, and they often constitute the chief cause of the patient's disability.

Another marked effect which merits closer attention is the *clawing of the*

toes, which it will be readily admitted is almost invariably found in this type of foot. The mere form of the high-heeled shoe, i.e., the necessary angulation at the junction of sole and instep, obviously determines some degree of dorsiflexion of the proximal phalanx, but a further factor of much greater importance, which seems to have escaped notice, is the displacement of the well-developed fibro-fatty pads (which nature provides under the metatarsal heads as under other pressure points, e.g., the heel) forwards under the digits (fig. 5). These masses of fat appear to be rolled forwards by the metatarsal heads much as dough is heaped up in front of the advancing rolling pin. In this connexion it must be remembered that whereas the 1st metatarsal is provided with a special joint on its plantar aspect where it articulates with the sesamoids, the other metatarsal heads have no such provision. As the metatarsals rise to the "take-off" position therefore the 1st metatarsal undergoes a movement of pure rotation about its head as an axis, but the others have to roll forwards so that there is an actual movement of the whole head forwards. It is this, in my opinion, that is responsible for the heaping-up of the fibro-fatty tissues in front of the heads, especially of the 2nd and 3rd metatarsals.

Examination of these feet will reveal the toes with their distal phalanges flexed over a thick roll of fat lying under the proximal phalanges, whilst the heads of the metatarsals are unduly exposed and easily palpated through the thinned overlying tissues of the sole, even although callosities are present. Lacking their normal padding the heads become sensitive to pressure and it is not surprising that patients so often say that they feel as if walking on bare bones.

SOME MINOR DISABILITIES

Secondary to the clawing, other minor painful conditions occur on the toes, such as subungual corns, end pressure on, and deformities of, the nails, dorsal corns, and bursæ over the prominent interphalangeal joints, and so on.

There are other sequelæ to the wearing of high heels, of less importance, but deserving of mention. The rim of the shoe presses unduly upon the tissues over the lower end of the tendo Achilles and there produces a callosity and sometimes a small bursa. Similarly, when a Court or strapped shoe is worn, pressure occurs anteriorly at the edge of the shoe or the strap, especially over the prominent tendon of the extensor longus hallucis, again with the production of corns or callosities.

High-heeled shoes always have a very small area of contact of heel with ground and this conduces to instability with a tendency to "turn" the ankle, a common cause of many a sprained ankle.

PALLIATIVE MEASURES

This recital of the consequences of wearing high heels is formidable enough, and there can be little doubt that there is nothing to be said medically in favour of such a fashion. It is a pity that the public cannot be induced to

the first, at others the second, and rarely the third is the most prominent head and therefore has to sustain the main portion of the stress. This question is further complicated by the fact that at an early stage the force

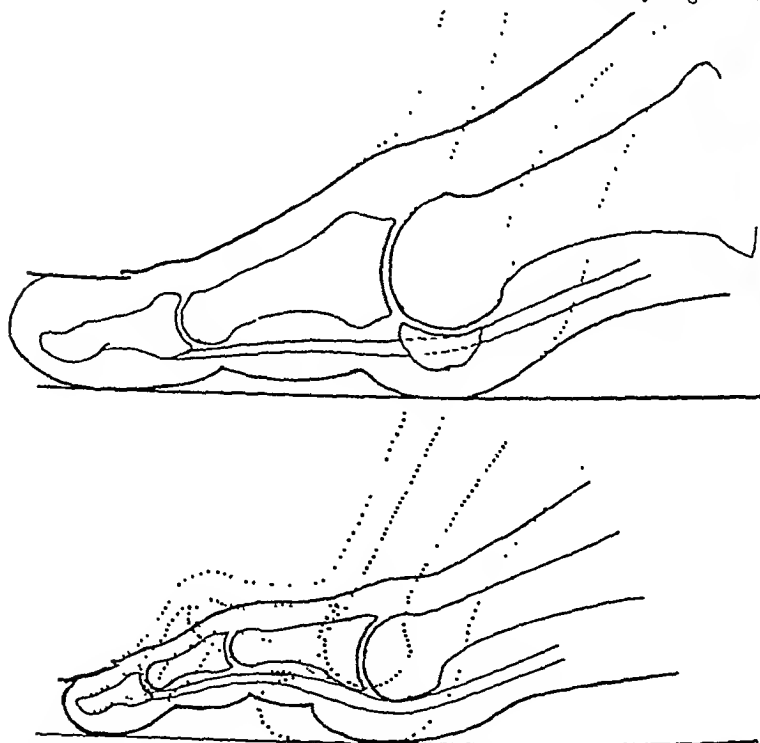


FIG. 5a and b.—Diagrams to illustrate the rolling movements of the heads of the metatarsals. The interrupted lines show the position assumed at the take-off. The upper drawing represents the great toe and the lower one the outer toes. The forward rolling of the heads in the latter case leads to displacement of the fibro-fatty pad under the proximal phalanx, which it elevates, whilst the other phalanges are flexed over it.

produce some "splaying" of the foot. In particular the angle between the 1st and 2nd metatarsals increases, the first now deviating mesially. This throws it out of the functional axis of the foot and so, whatever their length and prominence, the second or second and third metatarsals now have to take the main strain. The deviation of the first metatarsal sets the stage for the development of a *hallux valgus*, in the etiology of which high heels thus play an important part, and especially, as I have shown elsewhere (*Brit. med. J.*, 1942, i, 31), if the foot is inherently weak when considered from an evolutionary point of view. The more immediate effect of these changes is to produce painful callosities under the 2nd or 2nd and 3rd metatarsal heads. These will be found in almost every woman who has worn high heels for any length of time, and they often constitute the chief cause of the patient's disability.

Another marked effect which merits closer attention is the *clawing* of the

PAINFUL FEET

By M. G. GOOD, M.D., L.R.C.P., L.R.C.S.Ed.

THE syndrome of "*painful feet*" is of great importance, particularly in the Army, since it gives rise to disturbance of locomotion. "The condition of flat feet in all its varying degrees is by far the commonest cause of doubtful efficiency" (i.e., in the Army) (Burkitt, 1941). According to Wood (1942) there is to be distinguished a large group of cases of painful feet, not remediable by operation, consisting mainly of: (1) acute foot strain; (2) early degrees of flat foot; (3) metatarsalgia with flat anterior arch (most common of all); and (4) short Achilles tendon.

CAUSAL FACTORS

The common denominator of the conditions enumerated above is a disturbance of function, i.e., patients are unable to walk, march or stand for several hours. It is noteworthy that the disturbance of function present in painful feet is due solely to pain. The syndrome of painful feet belongs to a group of diseases called by Leriche (1939) "*maladie de la douleur*", since pain is the cardinal symptom which alone is responsible for disturbed function.

Flat foot.—Textbooks tacitly imply that the pain or ache complained of by patients is due to the abnormal shape—fallen arches, *pes cavus*—of the foot; but so far as I am aware there is no convincing evidence for this assumption. On the other hand, some facts are known which do not seem to be in keeping with the current opinion. It is an established fact that many individuals never complain of painful feet although they have fallen arches. Burkitt (1941), who has studied this question in the Army, states that in his battalion thirty men reported sick with symptoms caused by fallen arches. But there were thirty-three other men with a marked degree of flat foot, as evidenced by footprints and appearance, who never complained, although they had been for route marches. Moreover, at least in my experience, it does not often happen that an officer reports sick because of this condition. Evidently there must be a great number of officers who have fallen arches, since this anomaly is very common.

It is therefore justifiable to draw the conclusion that the anomaly of flat feet is not the only cause of pain and therefore is not responsible for the disturbed function present in some of the individuals suffering from it.

MYALGIA

My experiences in the Army seem to confirm the view that in the majority of cases the syndrome of painful feet not accounted for by any organic disease is caused by a myalgia of the foot muscles (Good, 1938-42). This conclusion is supported by the results obtained by injecting procaine as a diagnostic test. In the case of myalgia, diagnosed by objectively defined

believe that a shoe with a lower heel of the Cuban type, with a height of $1\frac{1}{2}$ or at most 2 inches, can be made to look quite smart and neat; with such heels the late after-effects would be greatly diminished although not abolished entirely, for an inherently weak foot may deform under the strains of locomotion even in rational footwear.

This article is not concerned with the treatment of the various resulting deformities, but it must be emphasized that when patients first present themselves for relief the conditions have usually been too long established to permit of radical replacement, nor can high heels be abandoned immediately, owing to the "set" of the foot. The most that can be done is to afford as much ease as possible by palliative measures, sometimes surgical, sometimes chiropodial.

The *common callosities* under the metatarsal heads (chiefly 2 and 3) must be skived down and a felt pad carefully cut to fit under the necks of the bones, thus distributing the pressures over a larger area in an attempt to prevent recurrence. A forward thinner extension of soft felt or sponge rubber under the metatarsal heads will to some extent take the place of the displaced fibro-fatty pads and so mitigate the sensation of "walking on bare bones".

Spreading or splaying of the metatarsals (especially 1 and 2) is a more difficult problem. The application of a metatarsal strap which encircles the foot is of value but it must not be made too tight or the circulation is obstructed. The straps may be of ordinary elastic strapping, of stout wide elastic or of webbing, the latter having the advantage of being removable for bathing. The effect of all these is increased by the wearing of laced shoes fitting snugly round the instep. It may be mentioned here that operative measures for the treatment of splay foot have been devised but they have proved to be generally unsatisfactory. Any attempt to wean the patient away from high heels must be done gradually; the heel may be dropped by about half an inch in each successive pair of shoes the patient wears until a $1\frac{1}{2}$ or 2 inch heel is reached; it is probably unwise in these cases to go lower than this.

The treatment of *hallux valgus*, although it is so often a result of high heels, is too extensive a problem to be dealt with in this article. *Clawing of the toes* is improved when the heel is lowered, but often demands in addition the use of felt pads, properly shaped, over the dorsum of the proximal phalanges. A fully trained chiropodist is taught how to cut and fit such pads. The operative treatment of clawed toes is rarely called for in cases of this type.

It is only too clear that the correct way to deal with these conditions is prevention, but there is little hope of doing this unless fashion can be made subservient to anatomical and physiological demands. This involves a difficult psychological problem that so far has defied solution.

The figures are reproduced from the author's book "The Foot" (3rd edition) by kind permission of Messrs. Baillière, Tindall & Cox.

PAINFUL FEET

By M. G. GOOD, M.D., L.R.C.P., L.R.C.S.Ed.

THE syndrome of "*painful feet*" is of great importance, particularly in the Army, since it gives rise to disturbance of locomotion. "The condition of flat feet in all its varying degrees is by far the commonest cause of doubtful efficiency" (i.e., in the Army) (Burkitt, 1941). According to Wood (1942) there is to be distinguished a large group of cases of painful feet, not remediable by operation, consisting mainly of: (1) acute foot strain; (2) early degrees of flat foot; (3) metatarsalgia with flat anterior arch (most common of all); and (4) short Achilles tendon.

CAUSAL FACTORS

The common denominator of the conditions enumerated above is a disturbance of function, i.e., patients are unable to walk, march or stand for several hours. It is noteworthy that the disturbance of function present in painful feet is due solely to pain. The syndrome of painful feet belongs to a group of diseases called by Leriche (1939) "*maladie de la douleur*", since pain is the cardinal symptom which alone is responsible for disturbed function.

Flat foot.—Textbooks tacitly imply that the pain or ache complained of by patients is due to the abnormal shape—fallen arches, *pes cavus*—of the foot; but so far as I am aware there is no convincing evidence for this assumption. On the other hand, some facts are known which do not seem to be in keeping with the current opinion. It is an established fact that many individuals never complain of painful feet although they have fallen arches. Burkitt (1941), who has studied this question in the Army, states that in his battalion thirty men reported sick with symptoms caused by fallen arches. But there were thirty-three other men with a marked degree of flat foot, as evidenced by footprints and appearance, who never complained, although they had been for route marches. Moreover, at least in my experience, it does not often happen that an officer reports sick because of this condition. Evidently there must be a great number of officers who have fallen arches, since this anomaly is very common.

It is therefore justifiable to draw the conclusion that the anomaly of flat feet is not the only cause of pain and therefore is not responsible for the disturbed function present in some of the individuals suffering from it.

MYALGIA

My experiences in the Army seem to confirm the view that in the majority of cases the syndrome of painful feet not accounted for by any organic disease is caused by a myalgia of the foot muscles (Good, 1938-42). This conclusion is supported by the results obtained by injecting procaine as a diagnostic test. In the case of myalgia, diagnosed by objectively defined

"myalgic spots", an injection of 1 to 2 ml. of procaine relieves pain immediately and restores disturbed function without delay.

Definition.—Foot myalgia is a muscular disease localized in anatomical parts—origin, insertion, course or edge—of the short muscles of the foot; rarely of muscles originating in the leg. The disease is characterized by what is termed *myalgic spots*: well and objectively definable areas of a muscle and its appendages—perimysium, tendon and ligaments. Sometimes it can be traced to a recent or previous injury (*traumatic myalgia*), but mostly it is of unknown, idiopathic origin.

Signs and Symptoms

Subjective.—(1) Pain or dull ache sometimes described as of a burning character referred to the sole, instep, dorsum of foot or heel.

(2) Sometimes paræsthesia—numbness, pins-and-needles—is present.

(3) Disturbed function: weakness or giving way of the ankle; inability to walk, march or stand.

Objective.—The objective signs centre round the "myalgic spots".

(1) The myalgic areas are, as a rule, localized in anatomical points of a muscle or muscles.

(2) Pressure on a myalgic spot elicits an extremely severe, agonizing ("sharp") pain which persists for a few minutes after pressure has ceased. In contradistinction, pressure on a normal muscle produces a slight ("dull") ache which disappears immediately on cessation of pressure.

(3) The painful areas as mapped out by patients are of a referred or heterotopic character and do *not* coincide with the myalgic spots, of which they are unaware.

(4) Pressure on a myalgic spot elicits an involuntary jerking in a part of the body not pressed upon, e.g. head, or the patient makes a grimace.

(5) After appropriate treatment—injection of procaine into the myalgic spots—both local pain elicited by pressure and the referred pain disappear immediately and the function of the diseased muscle is restored.

The *diagnosis* of foot myalgia depends upon an accurate location of the myalgic spots as defined above.

Technique of locating myalgic spots.—Examination is best made with the right thumb, or alternatively with the index or third finger. Exercise hard pressure with the top of the finger on the origin, insertion along the border and course of the muscle or tendon to be examined. Wherever possible the muscle or tendon should be pressed against a bone. The pressure has to be made in such a way as to cause only moderate discomfort or slight pain when applied to a normal muscle. In my experience patients easily distinguish the difference between a normal muscle and a myalgic spot. Pressure on the latter elicits so agonizing a pain that the patient winces and sometimes says spontaneously: "You have got it, Sir".

In foot myalgia the myalgic areas are mostly found in the large toe, at the inner and outer side of the base of the first phalanx. The myalgic points are usually found in cases associated with flat foot and correspond to the insertion of flexor hallucis brevis. Less frequent are myalgic spots in the flexor digitorum brevis, in the middle of its course or, more often, and

Especially in cases associated with metatarsalgia, at the base of the first phalanx of the third and fourth toes. Rarely the abductor hallucis is affected. On the dorsum of the foot the spots are at the insertion—ligamentous parts—of the peroneus brevis and accessorius, and the insertion of the Achilles tendon; the latter is usually found in painful heel (see fig. 1).

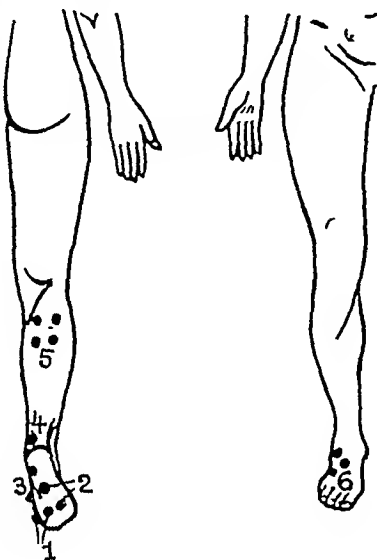


FIG. 1.—Localization of the most common myalgic spots in foot myalgia: (1) flexor hallucis brevis; (2) flexor digitorum brevis; (3) abductor hallucis; (4) Achilles tendon; (5) gastrocnemii; (6) peroneus brevis and extensor brevis digitorum.

Area marked with dots=myalgic spots.

plantar surface, i.e., in the flexor hallucis brevis, the flexor digitorum

TREATMENT OF THE MYALGIC FOOT

A rapid, effective and apparently permanent relief of pain can be obtained by injection of procaine into *each* myalgic spot, care being taken to infiltrate the whole affected muscular area. The solution used is:—

Procaine hydrochloride 2.0 g.
Chlorbutol 0.5 g.
Saline to 100.0
Sterile, in rubber-capped bottle

Technique.—The myalgic spots are mapped out very carefully on the skin with a blue dermatograph; the pencil marks are painted over with iodine and 1 to 2 ml. of procaine injected *intramuscularly* into each spot.

RESULTS OF TREATMENT

In about 62 per cent. of 100 cases the diseased muscles were found at the

TABLE I
100 cases of "painful feet"

No.	Muscle affected	No. of cases
1	Flexor hallucis brevis	40
2	Peroneus brevis	15
3	Flexor digitorum brevis	12
4	Achilles tendon	12
5	Abductor hallucis	10
6	Gastrocnemii	3
7	Other muscles	8
Total number of cases		100

brevis and the abductor hallucis, diminishing in that order. In 27 cases the muscles were on the dorsum of the foot, that is, the peroneus brevis and

"myalgic spots", an injection of 1 to 2 ml. of procaine relieves pain immediately and restores disturbed function without delay.

Definition.—Foot myalgia is a muscular disease localized in anatomical parts—origin, insertion, course or edge—of the short muscles of the foot; rarely of muscles originating in the leg. The disease is characterized by what is termed *myalgic spots*: well and objectively definable areas of a muscle and its appendages—perimysium, tendon and ligaments. Sometimes it can be traced to a recent or previous injury (traumatic myalgia), but mostly it is of unknown, idiopathic origin.

Signs and Symptoms

Subjective.—(1) Pain or dull ache sometimes described as of a burning character referred to the sole, instep, dorsum of foot or heel.

(2) Sometimes paræsthesia—numbness, pins-and-needles—is present.

(3) Disturbed function: weakness or giving way of the ankle; inability to walk, march or stand.

Objective.—The objective signs centre round the "myalgic spots".

(1) The myalgic areas are, as a rule, localized in anatomical points of a muscle or muscles.

(2) Pressure on a myalgic spot elicits an extremely severe, agonizing ("sharp") pain which persists for a few minutes after pressure has ceased. In contradistinction, pressure on a normal muscle produces a slight ("dull") ache which disappears immediately on cessation of pressure.

(3) The painful areas as mapped out by patients are of a referred or heterotopic character and do *not* coincide with the myalgic spots, of which they are unaware.

(4) Pressure on a myalgic spot elicits an involuntary jerking in a part of the body not pressed upon, e.g. head, or the patient makes a grimace.

(5) After appropriate treatment—injection of procaine into the myalgic spots—both local pain elicited by pressure and the referred pain disappear immediately and the function of the diseased muscle is restored.

The *diagnosis* of foot myalgia depends upon an accurate location of the myalgic spots as defined above.

Technique of locating myalgic spots.—Examination is best made with the right thumb, or alternatively with the index or third finger. Exercise hard pressure with the top of the finger on the origin, insertion along the border and course of the muscle or tendon to be examined. Wherever possible the muscle or tendon should be pressed against a bone. The pressure has to be made in such a way as to cause only moderate discomfort or slight pain when applied to a normal muscle. In my experience patients easily distinguish the difference between a normal muscle and a myalgic spot. Pressure on the latter elicits so agonizing a pain that the patient winces and sometimes says spontaneously: "You have got it, Sir".

In foot myalgia the myalgic areas are mostly found in the large toe, at the inner and outer side of the base of the first phalanx. The myalgic points are usually found in cases associated with flat foot and correspond to the insertion of flexor hallucis brevis. Less frequent are myalgic spots in the flexor digitorum brevis, in the middle of its course or, more often, and

especially in cases associated with metatarsalgia, at the base of the first phalanx of the third and fourth toes. Rarely the abductor hallucis is affected. On the dorsum of the foot the spots are at the insertion—ligamentous parts—of the peroneus brevis and accessorius, and the insertion of the Achilles tendon; the latter is usually found in painful heel (see fig. 1).

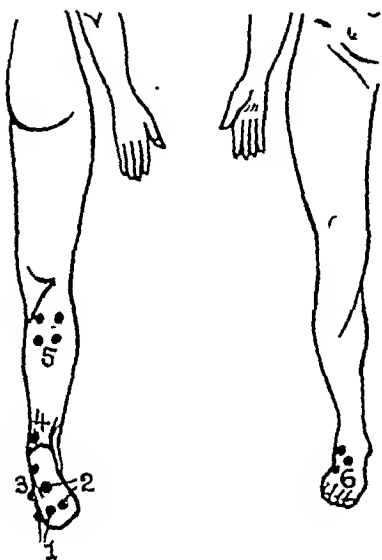


FIG. 1.—Localization of the most common myalgic spots in foot myalgia: (1) flexor hallucis brevis; (2) flexor digitorum brevis; (3) abductor hallucis; (4) Achilles tendon; (5) gastrocnemii; (6) peroneus brevis and extensor brevis digitorum.

Area marked with dots=myalgic spots.

plantar surface, i.e., in the flexor hallucis brevis, the flexor digitorum

TREATMENT OF THE MYALGIC FOOT

A rapid, effective and apparently permanent relief of pain can be obtained by injection of procaine into *each* myalgic spot, care being taken to infiltrate the whole affected muscular area. The solution used is:—

Procaine hydrochloride 2.0 g.
Chlorbutol 0.5 g.
Saline to 100.0
Sterile, in rubber-capped bottle

Technique.—The myalgic spots are mapped out very carefully on the skin with a blue dermatograph; the pencil marks are painted over with iodine and 1 to 2 ml. of procaine injected *intramuscularly* into each spot.

RESULTS OF TREATMENT

In about 62 per cent. of 100 cases the diseased muscles were found at the

TABLE I
100 cases of "painful feet"

No.	Muscle affected	No. of cases
1	Flexor hallucis brevis	40
2	Peroneus brevis	15
3	Flexor digitorum brevis	12
4	Achilles tendon	12
5	Abductor hallucis	10
6	Gastrocnemii	3
7	Other muscles	8
Total number of cases		100

brevis and the abductor hallucis, diminishing in that order. In 27 cases the muscles were on the dorsum of the foot, that is, the peroneus brevis and

Achilles tendon. In three cases a gastrocnemius myalgia was responsible.

The results obtained by injection of procaine are very gratifying. Often complete relief of pain and restoration of function were obtained by one treatment. Only rarely were more than two to three injections necessary for complete relief. It is noteworthy that a myalgic spot objectively located and properly injected no longer gives rise to complaints. If more than one treatment is found necessary it is due to one of the following reasons: (1) not *all* myalgic spots were injected; (2) faulty technique with regard to location or injection, or (3) aggravation of pain by the patient. With regard to permanent results I should like to refer to 26 cases kept under observation for several months. The results were as follows:—

Four men refused treatment; of the 22 officers and other ranks treated, 13 were "cured", i.e., they reported having no complaints, 9 men did not report after the last treatment although ordered to do so in two days.

It is worth stressing that none of the patients reported sick again because of foot complaints during the following period extending up to four to five months. It would therefore seem that the permanent results of the treatment are also satisfactory.

SUMMARY

Experience obtained in the Army in a large number of cases seems to confirm the view that the syndrome of painful feet, whether or not associated with flat foot or similar anomalies, is not infrequently due to a muscular disease of the foot—*foot myalgia*. The muscles commonly affected are the flexor hallucis brevis, the flexor digitorum brevis, the pronator brevis, and the Achilles tendon. The objective signs centring round the "myalgic spots" which can be located by objective criteria are described. Injection of procaine is recommended for relieving this pain, restoring the function of the diseased muscles in a short time, and leading to a rapid cure. It is suggested that the injection of procaine be used in all cases of painful feet, not accounted for by any organic disease, as a diagnostic test in order to prove conclusively whether or not a given pain is of muscular origin.

References

- Burkitt, R. T. (1941): *Brit. med. J.*, **i**, 967.
- Good, M. G. (1938): *Brit. J. phys. Med. N.S.*, **1**, 302.
- (1940a): *Ibid.*, **3**, 50.
- (1940b): *Lancet*, **ii**, 326.
- (1941): *The Practitioner*, **146**, 167.
- (1942): *Ibid.*, **148**, 236.
- (1942): *Ann. rheum. Dis.*, **3**, 118.
- Leriche, R. (1939): "The Surgery of Pain", London.
- Wood, H. L. C. (1942): *Proc. Roy. Soc. Med.*, **35**, 193.

THE NATURAL CURE OF AN ACUTE INTUSSUSCEPTION

AN UNUSUAL CASE HISTORY

By J. H. LOUW, CH.M.

From the Department of Surgery, University of Cape Town.

TITUS, a Bantu aged thirty years, became seriously ill in January 1941. Before this date he had been in good health although on occasions he had observed the presence of round worms in his stools. These he had regarded as "nyokas" (snakes), believing that he was "mpagati" (bewitched). Four days after the onset of this illness he started passing large quantities of blood per rectum. This brought him to the local doctor. He was now suffering from severe abdominal pain, incessant vomiting and marked prostration. His bowels had not acted normally for five days. He attributed all these symptoms to evil spirits.

The practitioner was faced by a patient *in extremis*. He was shocked and grossly dehydrated with sunken eyes, a dry hot skin and a parched tongue. His temperature was elevated, his pulse rapid and thready, and his abdomen was as tense as a drum and tender all over. Rectal examination revealed blood on the examining finger.

The diagnosis was only too obvious. Titus was suffering from the effects of advanced acute intestinal obstruction with severe water and salt depletion. The passage of blood per rectum suggested the diagnosis of acute intussusception, and the doctor urged his patient to go to hospital for an immediate operation. The African's superstitious mind, however, could not tolerate this advice. The native's distrust of the surgeon's knife is equalled only by his tremendous faith in the healing powers of the "nyanga" (witch doctor). Titus was most emphatic in his refusal, and he and his family departed forthwith to consult a "nyanga".

About a month later Titus again visited the practitioner. On this occasion he was hale and hearty, and beamed from ear to ear. Needless to say the doctor could hardly believe his own eyes.

Titus then related the rest of his story:—After they had left the practitioner he and his family had gone to the chief of all "nyangas" who, after much chanting and bartering, agreed to cure him of the evil spirits for the price of several head of cattle. Titus was given a large dose of the

"nyanga's" special "muti" (medicine) with the promise that it would drive all the evil spirits from his body. Following a very disturbed night during which he suffered severe pain and passed much blood per rectum, Titus passed the "Father and Mother of all nyokas". After that episode he gradually improved and ultimately completely regained his former strength.

Titus then produced the "master snake" which is illustrated in fig. 1.



FIG. 1.—Gangrenous portion of small intestine, measuring ten inches in length, passed per rectum.

COMMENTARY

The mechanism of this remarkable natural cure and the obstacles that have to be overcome before it can be effected, will be understood from a brief consideration of the pathological processes involved. During the course of an intussusception, as the invagination of proximal into distal intestine proceeds onwards, there is not only a progressive intestinal obstruction, but also a drag on the mesentery. This results in congestion at the neck of the intussusception, until finally the veins become completely compressed. Such

compression leads to œdema and swelling of the intussusceptum and ultimate interference with the arterial supply, resulting in destruction of the invaginated portion. Ulceration occurs at the neck of the intussusceptum leading to perforation and the development of a localized peritonitis. If the patient does not succumb to the effects of intestinal obstruction and infection, the whole of the inverted portion later becomes gangrenous and sloughs away. The separation occurs at the ring of constriction where the inverted portion enters. As a rule, perforation occurs at the time of separation, leading to rapid extravasation of the bowel content and a spreading peritonitis. Ulceration into large vessels with a massive hæmorrhage is also likely to occur at the time of separation.

Very rarely a natural cure may result. In such cases, before the separation, the entering and ensheathing layers become adherent due to a low-grade plastic peritonitis. After separation of the slough, which is then passed per rectum, the resulting raw surfaces are healed by fibrous tissue. It is clear, however, that this happy state of affairs can occur only if the patient is fortunate enough to survive all the following hazards: (1) the effects of intestinal obstruction; (2) local perforation with peritonitis; (3) massive perforation with generalized peritonitis; (4) severe secondary hæmorrhage.

Hence, as pointed out by Rutherford Morison, "it is the rule, with a few exceptions, that these patients die unless an operation can be performed, and the earlier this is done, the better".

I wish to thank Mr. F. du Toit van Zyl, acting Professor of Surgery, for permission to publish the case, and Dr. S. Disler, of the Addington Hospital Durban, for the details of the case history.

NATIVE AFRICAN MEDICINE

IN an article on native African medicine (*Pharmaceutical Journal*, August 13, 1949, 163, 128) E. C. Lum states that "modern medicine is slowly overcoming the ancient prejudices of the 'medicine man' or 'witch doctor' in Southern Africa, but it will be a long, hard battle, as is evidenced by a recent report from Johannesburg to the effect that the self-styled African National Herb Doctors' Association of South Africa is seeking official status for 'medicine men' . . . In general, the native considers disease as something from the outside which can be washed off or eliminated, and the methods used by their 'doctors' bear witness to this idea". "Medicine men" fall into two categories: the "doctor of bones", and the "witch doctor". The latter uses many herbs, roots and barks, and it is of interest to note that in the treatment of worms, which are prevalent among the natives, *Hibiscus trionum*, *Aloe tenuior*, and *Rumes ecklonianus* are among the plants employed.

CURRENT THERAPEUTICS

XXI.—PROTEIN HYDROLYSATES

By JOHN BEATTIE, M.D., D.Sc.

Bernhard Baron Research Professor, Royal College of Surgeons, England.

HYDROLYSED protein can be utilized in the body in exactly the same way as whole protein. It is prepared either by hydrolysing the protein molecule to amino-acids or small peptides, or by using either acid or a proteolytic enzyme. Acid hydrolysis has the advantage that in the process no organic material has to be added to the protein, and consequently hydrolysis can be effected easily under sterile conditions. Unfortunately, such hydrolysates cannot be used without adding to them adequate quantities of certain amino-acids which, although present in the protein molecule, have been destroyed by treatment with acid. Enzymic hydrolysates contain all the amino-acids present in the parent protein, but they are difficult to prepare without bacterial contamination of the hydrolysate.

Hydrolysates may be used as protein substitutes, but they possess no nutritional superiority over whole protein. They may be given by the oral route, but their taste and smell are unpleasant and preclude them from being swallowed in sufficiently large quantities to be of value. On the other hand, they can be given by nasal tube passed into either the stomach or duodenum. If the rate of inflow is controlled so that about 120 to 200 ml. per hour of the hydrolysate solution are passed into the duodenum or stomach they are tolerated fairly well. It must, however, be pointed out that there are few clinical conditions in which their use by the oral route is justified. Such conditions are: (1) ileostomy, when it is desired to obtain adequate absorption in the intestine above the stoma, and as little residue as possible in the discharge from the stoma; (2) deficiency of proteolytic enzymes such as might be found in fibrocystic disease of the pancreas; and (3) colonic conditions, when it is desirable to reduce the residue arriving in the colon.

SOLUTIONS AND DOSAGE

The same general principles apply to hydrolysates as apply to the whole protein. The amount of hydrolysate given must be adequate either for nitrogenous equilibrium or for positive nitrogen balance. For practical purposes 1 gramme of hydrolysate may be considered equivalent to 1 gramme of whole protein. Six grammes of glucose will be required for each gramme of hydrolysate given, and adequate quantities of vitamins must be available. Assuming that the patient weighs 60 kg. (132 lb.) and it is desired to achieve some measure of positive nitrogen balance while the patient is

confined to bed, then at least 75 g. of hydrolysate must be given and 450 g. of glucose. For oral use, the hydrolysate can be administered in a concentration of 7.5 g. per 100 ml. of water, and to this solution 5 g. of glucose can be added per 100 ml. The hydrolysate required can thus be provided in 1 litre of fluid in which 50 g. of glucose can also be administered; 400 g. of glucose have, however, yet to be given, and this should be administered in 10 per cent. solution, preferably made up in half-normal saline. This solution can be used to carry the necessary vitamins. The solutions required are:—

(1) *Hydrolysate solution*: 75 g. of hydrolysate powder to 1 litre of water.

(2) *Glucose solution*:

Glucose	400 g.
Thiamin (vitamin B ₁)	20 mg.
Riboflavin	20 mg.
Nicotinic acid	50 mg.
Ascorbic acid	150 mg.
Sodium chloride	18 g.
Water	4 litres

The solution for the drip-feed is made up by adding the hydrolysate solution to the glucose solution and mixing well. One-litre portions are measured out into litre or half-litre transfusion flasks, stoppered and kept in a refrigerator until required. These solutions should not be kept for longer than thirty-six hours. The administration should be carried out as for a continuous saline infusion. A drop counter and screw clip are necessary to control the rate of inflow, which should not exceed 500 ml. of the mixed solution per hour. Some patients cannot tolerate this mixture because of its nauseating taste, but this can be minimized somewhat by adding some celery flavouring to the mixture.

Diarrhoea is a not infrequent consequence of hydrolysate feeding. It can be abated if not stopped by using the following mixture:—

(1) *Hydrolysate solution*: 75 g. to 1 litre of water.

(2) *Glucose solution*:

Glucose	200 g.
Vitamins and salt as in previous glucose solution	
Water ... to	2 litres

(3) *Starch solution*:

Cornflour	220 g.
Water ... to	2 litres

The cornflour is made into a thin paste and gradually diluted with the water. The mixture is brought to the boil slowly and kept at boiling point for fifteen minutes. It is then allowed to cool. The solutions are mixed and measured out into litre bottles. The mixture is used as described above.

INTRAVENOUS ADMINISTRATION

Protein hydrolysates are available for intravenous administration. They are usually prepared in 5 per cent. concentration in a 5 per cent. glucose solution, sterilized and ready for injection. A daily requirement of 75 g. of hydrolysate could be met by giving 1.5 litres of hydrolysate solution, but the greater part of the hydrolysate administered will be used as a source of energy unless more glucose is given. In a ratio of 6 calories from glucose to 1 calorie from protein (as hydrolysate) it would be necessary to give 450 g. of glucose: 50 g. would be available in the solution of glucose and hydrolysate, leaving 400 g. more to be provided. In 5 per cent. solution it would be necessary to give an extra 8 litres of fluid. Obviously the infusion of 9.5 litres of fluid per twenty-four hours would be impossible. If the upper limit of fluid infusion per day be taken as 5 litres, it would be possible to provide 250 g. of glucose and 50 g. of hydrolysate in this volume. One litre of 5 per cent. hydrolysate in 5 per cent. sterile glucose solution and 4 litres of sterile 5 per cent. glucose are mixed in a sterile container and transferred to five 1-litre containers. The containers are stoppered and stored in a refrigerator until required. It is not advisable to prepare more than that needed for twenty-four hours.

Administration.—Infusion of the hydrolysate-glucose mixture is begun slowly into a vein. The point of the infusion needle should lie in a vein through which blood is flowing rapidly. Rapid blood flow is ensured by keeping the limb warm. After 10 to 15 ml. of fluid are run in over a period of five minutes, the infusion is stopped for about five minutes. If no reaction is observed a further 50 ml. are infused slowly at the same rate. Signs of a reaction are headache, and sense of chill followed by shivering which may, in a severe reaction, develop into a rigor, pallor and sweating. A reaction is almost invariably due to the presence of pyrogens in the saline. If a reaction is absent after the infusion of the 50 ml. portion, the infusion is continued at the rate of 250 ml. of the mixture per hour. At this rate the 5 litres of fluid can be distributed over 20 hours, thus ensuring maximum utilization of the hydrolysate. Too rapid infusion of the mixture may cause headache and muscular pain.

Intravenous hydrolysate infusions are justifiable only when it is impossible to provide protein or hydrolysate by the oral route. They should not be undertaken unless continuous supervision of the patient and of the inflow can be given. If they are continued for more than two days, steps must be taken to provide vitamins in the quantities set out for oral hydrolysate feeding (p. 237). These should be added to the glucose solution before the latter is sterilized by passing it through a bacterial filter. Pure synthetic preparations of these vitamins are available. It must be realized that the infusion of 50 g. of hydrolysate and the glucose to supplement it (250 g.) can provide only 1200 calories per day, which will be less than the basal energy requirements of an adult. Extra energy may be made available by the rectal administration

of glucose solutions, although the amount of glucose absorbed by this route may be small. The real difficulty in parenteral feeding is to provide for the calorie requirements of the patient. When it becomes possible to add to the infusion fluids quantities of emulsified fats which can be utilized and will not form emboli, this difficulty will disappear. So far no safe preparation has been devised.

It is obvious that in the treatment of the convalescent patient, protein hydrolysates given by vein have no place. They have a value in the pre-operative and immediate postoperative phases and in a limited number of other clinical conditions. Their use requires considerable care, apart from the difficulties inherent in any continuous intravenous infusion. Water and salt balance must be watched to ensure that water and salt retention do not occur. The urine output should be measured and the volume should be within 500 to 600 ml. of the fluid administered. A more accurate control can be obtained by estimating the daily chloride intake and output. These two values should balance within 1 gramme.

PLASMA AS A FOODSTUFF

Plasma infusions have been used successfully to restore the blood volume to normal and to maintain it. They can, however, be used to provide all or part of the protein requirements of the body. Before operation, such infusions can assist materially in reinforcing the protein reserves and may bring about a high positive protein balance. The plasma proteins so provided usually do not enter at once into metabolic processes: when they do, the rate at which proteins are broken down is not accelerated materially. They thus differ from the change in metabolism brought about by the infusion of protein hydrolysates. These hydrolysates enter at once into metabolic processes and accelerate them. The oxygen consumption rises and the urinary nitrogen is increased mainly by the increased production of urea from the amino-acids in the hydrolysates. This increased metabolic activity may be beneficial when there is a depressed metabolism but may be harmful when the catabolic response is already well established.

After operation, in the catabolic phase in disease, and after injury, infused plasma proteins may be of great value. Because they do not accelerate markedly the general level of metabolism as do proteins fed by mouth and hydrolysates by vein, they mitigate the drain on the body proteins. As plasma can be administered by vein in concentrations higher than normal, it is possible to give a high protein intake in a relatively low volume. This advantage, however, is to some extent diminished by the need for providing carbohydrate to prevent the use of the plasma protein as a source of energy. As there is usually no great acceleration of metabolism when plasma proteins are given by vein, it is possible to obtain a good protein-sparing action by less carbohydrate than would be necessary with hydrolysates. The following mixtures have been found of value. The first is designed to main-

tain a patient in bed in nitrogenous equilibrium or in slight positive nitrogen balance before operation. The second aims at a small positive nitrogen balance under the same conditions. In the catabolic phase the second mixture may be used with advantage.

Mixture 1

Dried plasma protein 70 g. in 500 ml. of water.

Glucose 200 g. in 3500 ml. of half-normal saline.

The protein solution (sterile) is made up and after the protein is in solution the sterile glucose solution is added to it. The mixture is then transferred into 1-litre transfusion flasks and kept in a refrigerator until required. It is not advisable to prepare at one time more than that required for twenty-four hours. The solution is infused slowly and if possible continuously over the whole twenty-four hour period. The rate of infusion should not exceed 300 ml. per minute.

Mixture 2

Dried plasma protein 100 g. in 500 ml. of water.

Glucose 300 g. in 4000 ml. of half-normal saline.

The mixture is prepared as for mixture 1. The rate of infusion should not exceed 300 ml. per minute.

The use of plasma-glucose mixtures should not be prolonged beyond three days unless the urinary volume and chloride excretion are measured. If the urinary volume is within a litre of the volume infused and the daily chloride excretion approximates closely to the total chloride in the infusion mixture, there is no danger from water retention. When possible the daily urinary nitrogen output should also be measured and compared with the nitrogen provided in the plasma proteins. The state of the nitrogen balance is the only guide to the efficiency of this method of feeding.

Plasma proteins can be administered by gastric or duodenal tube, but human plasma is unnecessary, as dried bovine plasma may be substituted and is equally effective. The mixtures suggested for hydrolysate feeding by tube may be employed by substituting for the hydrolysate powder in them an equal quantity of dried bovine plasma or bovine albumin. These mixtures do not possess any nutritional advantage over the solutions of natural foodstuffs recommended for tube feeding. They are, however, completely fat-free and are tolerated better than hydrolysate solutions.

PLASMA SUBSTITUTES

Plasma substitutes were devised to increase and maintain the plasma volume until either human blood or plasma could be given or the patient could produce plasma protein in quantities sufficient to meet his needs. In convalescence their value depends upon their ability to supply the protein required in metabolism. Plasma substitutes such as acacia and pectin, being complex carbohydrates, are valueless because they contain no protein. Animal gelatin in its "degraded" or short molecule form has been used successfully as a plasma substitute. Unfortunately, its value as a protein

nutrient is poor as it does not contain all the essential amino-acids. It has, however, been claimed (Brunschwig *et al.*, 1943a, b) that daily intravenous infusions can bring about a positive nitrogen balance. It is inefficient, for a considerable quantity of the infused gelatin may be excreted in the urine. Brunschwig and Nichols (1944) estimate this loss at about 60 per cent., and Jacobson and Smyth (1944) as high as 80 per cent. within forty-eight hours. Pseudo-agglutination and increased sedimentation rate occur after gelatin infusions, and a definite anti-thrombin action has been observed (Haimovici and Fine, 1945). These disadvantages reduce its value as an aliment by the intravenous route. The use of fish gelatin (isinglass) has been advocated by the Toronto school (Taylor and Waters, 1941; Taylor and Moorhouse, 1943; Pugsley and Farquharson, 1943). They claimed a low incidence of febrile reactions and presented some evidence in favour of the utilization of the material as a source of body and plasma protein. At present it is not possible to evaluate isinglass as a nutrient for intravenous use in convalescence. The use of bovine plasma proteins as aliments by intravenous infusion is still experimental. In spite of painstaking work, Cohn and his collaborators (1942) have not succeeded in freeing bovine albumin from antigens. At present therefore it has no place in convalescent treatment.

Intravenous infusions, however, are not the only method of providing nutrients. The oral route, when it can be used, is still the most simple, and except in rare cases protein so administered is absorbed to the extent of 90 per cent. It has been suggested already that bovine plasma or albumin may be given by gastric or duodenal tube in solution with glucose or starch. It is readily absorbed and enters rapidly into metabolic processes, the urinary nitrogen rising within two hours. The low cost of bovine plasma (dried) and bovine albumin, compared with that of human plasma (dried) is an advantage, but it is still great compared with the equally suitable proteins in milk. Solutions of spray-dried skimmed milk are as effective nutritionally as dried human or bovine plasma.

References

- Brunschwig, A., and Nichols, S. (1944): *Surgery*, 16, 923.
——, Corbin, N., and Johnston, C. D. (1943a): *Ann. Surg.*, 118, 1058.
——, Scott, V. B., Corbin, N., and Moe, R. (1943b): *Proc. Soc. exp. Biol. N.Y.*, 52, 46.
Cohn, E. J., *et al.* (1942): "Blood Substitute and Blood Transfusion", Springfield, Illinois.
Haimovici, H., and Fine, J. (1945): *New Engl. J. Med.*, 233, 8.
Jacobson, S. D., and Smyth, C. J. (1944): *Arch. intern. Med.*, 74, 254.
Pugsley, H. E., and Farquharson, R. F. (1943): *Canad. med. Ass. J.*, 49, 262.
Taylor, N. B., and Moorhouse, M. S. (1943): *Ibid.*, 49, 251.
——, and Waters, E. T. (1941): *Ibid.*, 44, 547.

REVISION CORNER

CONSTIPATION IN INFANCY AND CHILDHOOD

THE term constipation is not infrequently misused to denote infrequency in evacuation of the bowels, and in this restricted sense the diagnosis is often wrong. The derivation of the word gives its true meaning and the word constipation should be used only in reference to the character of the motion when it is condensed, too firm and too dry. Faeces in this state is difficult to evacuate and there is usually some delay, but delay or infrequency of defaecation does not always imply constipation.

In infancy it is by no means uncommon for an infant to pass only one motion a day at an age when the average is two or three. This often causes maternal anxiety, which can be dispelled by finding a motion of sufficient size and of normal consistency. Infrequent bowel action is of no importance if the character of the motion is consistently soft, ample, easy of evacuation, of good colour (ranging from the scrambled egg of early infancy to light brown). In contrast, the state of constipation is present, despite a daily evacuation, when the action is difficult by reason of the bowel content being too firm, too dry and too small in bulk. From these facts it follows that the diagnosis of constipation can only be made from an inspection of the stools. The frequency factor depends upon the vagus activity, and when vagotonia or sympatheticotonia is inherent, defaecation on alternate days only is still consistent with health provided the motion is normal in character for the age.

CAUSES AND PREVENTION

Few, if any, infants or children do not experience occasional constipation and the most common cause is undoubtedly temporary insufficiency of fluid intake, or following excessive fluid output which is occasioned by excessive sweating due to overheating, pyrexia or oedema, or after dehydration from vomiting, diarrhoea and diuresis, with loss of mineral salts and derangement of the osmotic process in the bowel.

The first essential to correction of any tendency to constipation is the provision of an adequate fluid intake, for the normal stool is about 80 per cent. water in early years. Water is of much greater importance in childhood than in later life when the fluid retention mechanism is fully developed. The daily water requirements per kg. ($2\frac{1}{4}$ lb.) of body weight under ordinary conditions varies with the age: in the neonatal period at the third day it is 80 to 100 ml.; at the tenth day, 125 to 150 ml.; at three months, 140 to 160 ml.; at six months, 130 to 155 ml.; at nine months, 125 to 145 ml.; at one year, 120 to 135 ml.; and thereafter the amount decreases to 70 to 85 ml. by the tenth year.

IN INFANCY

After the patency of the alimentary tract has been proved beyond question by the passage of meconium and normal stools in the second week, inquiry into the daily fluid intake is the first step in the treatment of constipation, and this is especially important in dealing with infants fed by artificial methods. Constipation is rare in breast-fed infants. Inadequate quantity of milk is the most common cause of constipation in infants, and in breast-fed infants test feeds should be made to ascertain the total daily intake. Roughly, an infant requires $2\frac{1}{2}$ oz. (70 ml.) of fluid per lb. (0.45 kg.) of body weight daily. If the intake fulfils this requirement the error may lie in the amount of carbohydrates in the feed, and the addition of sugar is indicated in the form of dextrimaltose, which is less fermentable. Excess of fats may also result in constipation, the stools being light in colour, dry and greasy. Many coeliacs exhibit constipation.

In older infants too much milk and delay in introducing solid foods may be the error; on the other hand, too great a residue in the diet may be the fault.

Pain on evacuation is a deterrent to regular habits. When this results from spasm of the sphincter it is best treated by digital dilatation two to three times a day. When pain is a feature, examination for fissure and hæmorrhoids is needed. Colic, be it noted, may well arise from too frequent resort to cathartics.

Symptomatic constipation in infancy is seen in congenital incomplete obstruction, rickets, tabes mesenterica, malnutrition, nephritis, anæmia, and pyrexia, and as evidence of irregular training in evacuation of the bowel.

IN OLDER CHILDREN

Constipation in older children is seen chiefly as a result of laziness, over-eating, lack of fluids, unsuitable and stodgy meals, too much milk food, and lack of exercise. Discipline will cure most of these cases, along with correction of the diet and the addition of water and fruits, such as prunes, figs, dates, apricots, stewed apples, and vegetables of the green variety.

Very active youngsters of the sympatheticonic type are often subject to bowel stasis. Sweating induced by their abnormal vitality contributes by dehydration. Such children may require frequent aperients, but it is advisable to inspect the stools before assuming constipation to be present, despite negative days as regards evacuation of the bowel. A word is necessary in condemnation of the Victorian habit which still prevails of a Friday night purgative which upsets the rhythm of the bowel *often for two to three days in each week. The habitual use of laxatives is rarely necessary and much mischief in nutrition may follow the injudicious and intemperate use of suppositories, enemas and aperients.*

Obstipation or intractable constipation, is a useful term to denote those cases in which the bowel stasis is excessive. When this is a feature, hypothyroidism should always be borne in mind. Not a few cretins are missed in diagnosis because the other classical features are not very striking to the eye, and in these cases delay in treatment with thyroid gland may have permanent ill-results in physical development. It is a wise precaution to suspect hypothyroidism in all cases with habitual infrequent bowel action of more than two days.

Megacolon is the classical example of obstipation when bowel action may occur only at intervals of two and three weeks. Established cases present no difficulty in diagnosis, but it should be remembered that in many of these the bowel stasis is slowly developed and early recognition may greatly influence the prognosis. Diabetes insipidus has marked constipation as a feature, but this state is extremely rare in childhood.

Congenital abnormalities of the bowel account for certain cases of constipation. There may be a daily evacuation of the bowel which is inadequate, and every ten days or so an immense evacuation of the bowel occurs, often unformed and surprisingly large. Malrotation of the bowel and abnormal bands and kinks result in recurrent delay and obstruction which in marked cases is accompanied by colic, and maybe vomiting. Many mild degrees of these abnormalities pass by unnoted for years.

CONCLUSION

Constipation may be classified into three groups: acquired, symptomatic, and congenital; and the measures to be adopted depend upon the cause. Diligent inquiries for dietetic errors should be made and correction applied. Simple sugar additions and decrease in fats with generous water intake will suffice in most infants. Habit formation should never be neglected and it should begin as soon as the idea can be appreciated. If dyspepsia accompanies the constipation, milk of magnesia may be used as a corrective. Drugs, although necessary at times, should be used sparingly, and among those time-honoured ones are grey powder, senna, rhubarb and phenolphthalein. Castor oil on occasions when a good single evacuation is indicated is still much favoured; liquid paraffin being an inert lubricant condones the mischief

and is justified in obstipation only. Suppositories and enemas are indicated only as occasional measures in acute constipation, and their routine use cannot be too strongly condemned.

BRUCE WILLIAMSON, M.D., F.R.C.P.

THE USE AND ABUSE OF AMPHETAMINE

AMPHETAMINE is the non-proprietary name adopted by the British Pharmacopœia for a synthetic drug chemically related to, and comparable in its pharmacological action with, ephedrine and adrenaline. In this country it is manufactured by several firms and marketed under a variety of proprietary names (table 1). The drug is obtainable only on the prescription of a registered medical practitioner or the signing of the Poisons Register.

TABLE 1
Some Proprietary Preparations of Amphetamine Sulphate

Name of Manufacturer	Proprietary Name of Drug
Allen & Hanburys Ltd., Bethnal Green, E.2. . .	Amphetamine sulphate tablets
British Drug Houses, Ltd., Graham Street, City Road, N.1	Tab. amphetamine sulphate
Burroughs Wellcome & Co., 12 Red Lion Square, W.C.1	"Methedrine" (d-N-methylamphet-amine hydrochloride) Inhaler
W. J. Bush & Co., Ltd., Ash Grove, Hackney, E.8	"Allodene"
Danancy & Co., Ltd., Harrow, Middlesex	Dextro-amphetamine sulphate (Tabs. D.24) Dextro-amphetamine sulphate 5 mg. with phenobarbital gr. $\frac{1}{2}$ (Tabs. D.25)
Evans Medical Supplies Ltd., Speke, Liverpool 19.. . . .	Tab. amphetamine sulphate
Gedeon Richter Ltd., Richter House, N.W.5 . .	Tab. amphetamine sulphate
Philip Harris Ltd., 144 Edmund Street, Birmingham 3	Tab. amphetamine sulphate Tab. dextro-amphetamine sulphate
C. J. Hewlett & Son Ltd., 35-43 Charlotte Road, E.C.2	Tab. amphetamine sulphate
Mathews & Wilson Ltd., 6-8 Cole Street, S.E.1	Amphetamine tablets
Medo-Chemicals Ltd., 178 Pentonville Road, N.1	"Amphamed": amphetamine sulphate
Menley & James Ltd., 123 Coldharbour Lane, S.E.5	"Benzedrine" tablets (racemic amphetamine sulphate) "Benzedrine" ampoules "Benzedrine" inhaler "Dexedrine" tablets (dextro-amphetamine) "Dexedrine" ampoules
United Chemists Assoc., Ltd. (Ucal), Ucal Works, Cheltenham Spa	Tab. amphetamine sulphate N.F.
Ward Blenkinsop & Co., Ltd., 6 Henrietta Place, W.1	Amphetamine sulphate tablets Dextro-amphetamine sulphate tablets
Wright Layman & Umney Ltd., 44-50 Southwark Street, S.E.1	Tab. amphetamine sulphate

Amphetamine has been employed on a large scale over a number of years and it is now possible to present accepted views on its value in a number of conditions. The first clinical report on its use was in the treatment of narcolepsy (1935), but it did not achieve popular recognition until the recent war when it was widely used

for abolishing fatigue during periods of temporary stress ("pep pills"). Its principal actions are stimulation of mental activity and abolition of physical fatigue. When applied locally, especially in the nose, it produces local vasoconstriction. Other effects, such as relaxation of the musculature of the alimentary tract, are less pronounced and are of little therapeutic value.

SIDE-EFFECTS

Amphetamine must now be accepted as a most valuable addition to modern therapeutics and, although its indiscriminate use should be discouraged, it is recognized as having a wide margin of safety with few toxic effects and little fear of addiction, provided reasonable care and supervision are exercised. Undesirable reactions may include restlessness, insomnia, palpitations, tachycardia, sweating, disturbed bowel action, mydriasis, diuresis, dryness of the mouth, and transient slight elevation of the blood pressure. These reactions, however, are uncommon and, although unpleasant, are never serious and are unlikely to occur unless given to a patient with anxiety symptoms. People of pyknic build appear to tolerate the drug better than the asthenic. More serious and even fatal reactions, such as aplastic anæmia, coma, and severe circulatory disturbance, have been described as exceptional occurrences, but in most of the published cases doubt has been expressed whether it was the amphetamine or some other factor which determined their onset. In the initial stages of treatment it is sometimes desirable to prescribe phenobarbitone at night to allay nocturnal restlessness and insomnia, and for the same reason amphetamine should not be taken orally later than midday, although in some conditions it may be necessary to administer the last dose at about 4 p.m.

CLINICAL USES AND DOSAGE

When prescribed in tablet form the average dose recommended is 10 mg. to 20 mg. daily, taken in two doses, one on waking and the other at 12 noon, but exact dosage and administration will vary with the individual and the nature of the condition treated. It is advisable to begin treatment with 2.5 mg. (half a tablet) to test for intolerance. The effects of oral administration are usually apparent in thirty minutes to three hours, the length of action ranging from three to nine hours. In normal subjects 10 mg. to 20 mg. of amphetamine taken orally *increases mental alertness*, speeds the flow of thought, promotes loquacity, stimulates muscular activity and diminishes fatigue. These properties determined its employment as "pep pills" in periods of stress to delay the need for sleep and meet the emergency of extreme fatigue, and it achieved a high reputation in the Armed Forces and Merchant Navy during the recent war. In the stress and strain of modern life it has much to commend its occasional use. It has been advocated for medical men roused from sleep to deal with a difficult situation, as it will promote mental alertness and ward off physical fatigue when most needed, to the advantage of all concerned. To meet such an emergency the dose recommended is 5 mg. or 10 mg. but it should not be repeated in less than eight hours, and not more than three such doses should be taken in the twenty-four hours. It must be appreciated that amphetamine does not abolish the need for sleep but only postpones it, and loss of sleep should be made good later.

The stimulating effect of amphetamine on psychic activity has earned for it a high reputation in the symptomatic control of several disorders of the central nervous system. In *narcolepsy* it may be regarded as a specific, and in this disease large doses may be required, e.g. 20 to 60 mg. daily, for lengthy periods and possibly for the remainder of the patient's life. It is of value in *epilepsy* in inhibiting the depressant and soporific effects of anticonvulsant drugs, particularly the hebetude of phenobarbitone, without impairing the control of the fits. It is of particular value in alleviating depression in *mild depressive states*, whether endogenous in origin or following on influenza and similar infections, or occurring in association with the

menopause, troublesome dysmenorrhœa, or senility. It is probably best known for its beneficial action in these disorders. It is not wise to prescribe it in cases of severe depression, in the presence of paranoid symptoms, or when marked anxiety features, extreme restlessness, or insomnia are present. Good reports have followed its use in lessening the depression, physical fatigue and oculogyral crises in *postencephalitic Parkinsonism*, and it is regarded as a useful therapeutic adjunct to the antispasmodic drugs usually employed in this disorder. Unfortunately, it has little beneficial effect when the cause of the Parkinsonian state is arteriosclerosis. Amphetamine is very effective in the control and treatment of *chronic alcoholism*, with the exception of alcoholic psychosis, whilst it is claimed that a single dose of 5 mg. or 10 mg. is efficacious in abolishing the "hang-over" symptoms of alcoholic over-indulgence. It has been employed successfully in the control of morphine and nicotine addiction, but such cases are likely to become addicted to the new drug. Good results have followed its use in some cases of *nocturnal enuresis* associated with heavy sleep, in which event the drug must be taken at bedtime, and also in the control of certain behaviour disorders of childhood. Success has been reported in lessening the symptoms of migraine.

Amphetamine has earned popular renown in the control of *obesity*. Undoubtedly it is of great value provided it is realized that the drug is only an adjunct to strict dieting. By lessening the appetite it encourages the obese patient to learn new dietary habits, which often remain even when the drug has been discontinued. It renders his lot more tolerable by alleviating depression, abolishing fatigue and promoting a sense of well being, whilst the resulting increased muscular activity encourages him to lead a more active and healthy life. Amphetamine alone does not produce any appreciable loss of weight. In such cases the recommended dose is 5 mg. taken before breakfast, repeated at 11 a.m. and again at 4 p.m., but occasionally 10 mg. may be permitted.

Finally, in the form of the inhaler, its local vasoconstrictor effect may be utilized in the symptomatic treatment of *rhinitis* and *sinusitis*, but unfortunately it is of no value in the control of allergic states such as hay fever and spasmodic asthma.

CONTRAINDICATIONS

The use of amphetamine is contraindicated in hypertension, coronary artery disease, manic excitement, and in the presence of known idiosyncrasy to the drug or to ephedrine. It should be employed with caution in the presence of vasomotor instability, insomnia, anorexia and loss of weight, and anxiety states.

LEONARD HOWELLS, M.D., F.R.C.P.

CARDIOSPASM

THE muscular ring encircling the lower end of the œsophagus, commonly known as the cardiac sphincter, is actually little more than a slight thickening of the œsophageal musculature; the ring is normally in a state of tonic contraction but relaxes with the approach of each peristaltic wave, so as to permit the passage of food into the stomach. The vagus nerve supply appears to exert an inhibitory influence, and section of the vagus nerve fibres causes spastic contraction of the lower end of the œsophagus; sympathetic nerve fibres supplying the "sphincter" appear to be predominantly excitatory. Failure of the cardiac sphincter to relax after deglutition results in dysphagia, and in time gives rise to dilatation of the lower portion of the œsophagus. This condition, often termed "cardiospasm", is better defined as achalasia of the cardiac sphincter.

DIAGNOSIS

The presenting symptom is invariably a complaint of food "sticking" behind the sternum, associated with retrosternal discomfort. Relief is afforded by bringing

to the greater part of what has been eaten, and the patient soon learns to do this voluntarily, in much the same way as a young infant regurgitates. The condition seldom gives rise to pain and nausea, and true vomiting does not occur. In the majority of cases the onset is insidious, and the history is of periodic bouts of discomfort and regurgitation. The attacks, at first transient, recur with increasing frequency and their duration gradually increases until the symptoms become persistent. By this time, loss of weight is apparent, and considerable quantities of stagnant food mixed with mucoid saliva are regurgitated. Regurgitation occurs particularly at night, shortly after retiring to bed, and although the patient may complain of the unpleasant taste of the regurgitated food it never tastes acid, and there is no associated "heartburn".

The history and description of symptoms are, in most cases, clearly indicative of obstruction at the lower end of the œsophagus. The clinician's task is primarily to decide the cause of the obstruction. In long-standing cases, the duration of symptoms will indicate achalasia rather than neoplasm. Absence of pain and heartburn also favour achalasia rather than neoplasm or œsophageal peptic ulcer, but the age of the patient is of little help in establishing the diagnosis; during the past year I have seen carcinoma of the œsophagus in two young men aged twenty-eight and thirty-four years, and œsophageal peptic ulcer in a child of twenty months. In the absence of a long history of recurrent attacks it is therefore essential to complete a barium skiagram, and in some cases œsophagoscopy may be necessary too. Before either of these investigations, the œsophagus should be emptied through a wide-bore rubber tube: the quantity of food and mucus withdrawn is often from 1 to 2 pints in long-standing cases of cardiospasm, whereas the volume of residue is considerably less when there is an obstruction due to neoplasm or spasm associated with peptic ulcer or œsophagitis. The presence of blood in the material aspirated is, of course, a clear indication of neoplasm or ulceration.

X-ray examination of the œsophagus should be made with a semi-thick barium paste; the typical picture is of a grossly dilated œsophagus with a regular outline, narrowing suddenly to end at the cardiac sphincter. There may be slight irregularity in the outline of the cardia, but as each additional mouthful of meal is swallowed, the cardia relaxes sufficiently to admit a thin trickle of barium. It is often possible to produce complete relaxation of the cardia by giving the patient an antispasmodic during the screening: inhalations of octyl nitrite are more effective than amyl nitrite, but in some cases it may be necessary to give other stronger preparations (1.0 to 1.5 ml. of a 10 per cent. solution of tetraethylammonium bromide, intravenously). These measures will, of course, produce relaxation in cases of spasm due to ulceration of the œsophagus, and it may then be possible to see the outline of the ulcer crater. If cardiospasm is secondary to carcinoma of the œsophagus or to secondary involvement of para-œsophageal glands, it is impossible to produce complete relaxation of the cardiac sphincter, and the outline of the lower end of the œsophagus remains persistently irregular. In some cases it may prove difficult to decide whether an ulcer is benign or malignant, in spite of careful screening, and such cases should be referred for œsophagoscopy. This investigation may also help to establish the diagnosis when extrinsic tumour is suspected (lymphatic glands and aneurysm being the most likely cause), and in some cases of cicatricial stricture and œsophagitis.

TREATMENT

If treatment is to be successful, it is essential to obtain the patient's full cooperation, and when dealing with intelligent patients it is as well to explain briefly what achalasia is and to reassure the patient, once cancer has been excluded. Antispasmodic drugs alone are quite useless as a therapeutic measure, but they do form a useful adjunct to treatment by passing mercury bougies. The bougies used,

Hurst's tubes, are fairly thick-walled rubber tubes, sealed at each end and half filled with mercury; the weight of the column of mercury forces the cardiac sphincter open. It is advisable to start with a small bougie, 24 gauge, which should be lubricated with glycerin or liquid paraffin. When passing a bougie for the first time, it is better to pass it with the patient behind the X-ray screen, so that the position of the tube can be checked radiologically by administration of sips of the barium paste. Once the patient has mastered the art of swallowing a bougie, he is soon able to tell when the tube has passed through the cardiac sphincter. The bougie should be passed before each meal and kept in position for fifteen to twenty minutes. Many patients find that an octyl nitrite inhaler or a trinitrin tablet administered just before the bougie is swallowed makes the procedure somewhat easier. The size of the bougie used should be increased by working up to a 30 or 34 gauge.

When the bougie has been passed regularly for two or three months it is often possible to reduce the frequency of this procedure to twice daily, preferably in the evening and on rising in the morning, and later to once daily, and then even weekly. During the initial stages of treatment, diet should be semi-solid, and food must, of course, be thoroughly masticated. The Sippy diet is seldom necessary except if there is œsophagitis as a result of prolonged stagnation of food in the lower œsophagus. Phenobarbitone may be used in the initial stages of treatment for nervous or apprehensive patients, but should not be continued once the patient is practised in the art of passing a bougie.

R. GWYN EVANS, M.B.E., M.D., M.R.C.P.

NOTES AND QUERIES

Postponement of Menstrual Bleeding

QUERY.—I should be obliged if you could give me information on the following problem: How best can the normal menstrual cycle be postponed for a few days in a normal healthy married woman, and what measures can be taken to procure this effect? Is it possible to obtain postponement by a method of treatment which can be given in the luteal, i.e. post-ovulatory, phase?, and if so, which drugs should be taken, and can they be administered by mouth? I am often questioned on this subject by Service personnel going on leave.

REPLY.—The normal menstrual cycle may be interfered with in the following ways:

(1) Large doses of œstrogen given as early as possible in the cycle will induce an œstrogen withdrawal bleeding within three or four days of discontinuing administration. For instance, 3 mg. of stilbœstrol given daily by mouth, beginning on the first to about the fifth day of the cycle will inhibit ovulation and produce a withdrawal bleeding three or four days after a ten to fourteen day course of treatment. This withdrawal bleeding, in the absence of further endocrine therapy, should be followed by normal cycles.

(2) After about the fifth day of the cycle, and certainly after the tenth day, it is not easy to influence the normal course of events. (a) Large doses of androgen, e.g. 50 mg. of methyl testo-

sterone daily, given until the day to which it is desired to postpone bleeding may produce the desired effect, but androgens have a marked individual variation in effectiveness, and one could not guarantee that they would achieve the result aimed at, especially if they were administered during the luteal phase of the cycle. (b) Very large doses of chorionic gonadotrophin, provided they are administered early in the luteal phase, might prolong this phase. They would have to be given intramuscularly in doses of, say, 5000 I.U. every second day until after the time at which it was desired to postpone bleeding.

Thus it is not at all easy to change the pattern of any particular normal, ovulatory, menstrual cycle unless there is an opportunity of doing so at the very beginning of the cycle.

PETER BISHOP, D.M.

Impotence and Diabetes

QUERY.—A male patient, aged thirty-four years, a diabetic on insulin for seven years, now complains of impotence for nine months accompanied by frequent attacks of testicular pains with very slight tenderness of the testicles. The pains have disappeared now that the impotence has asserted itself. Further, the patient gives a history of persistent masturbation dating back to puberty. Matrimonial life is happy, with two children. Previous to the diabetic state being

recognized the patient often had bouts of acute congestion of the liver, usually brought on by dietary indiscretions, such as consumption of eggs, fats, rhubarb, cucumber, ice cream, and worry causing digestive upset. Since the diabetic state has become controlled, these foods no longer produce "liver" symptoms. There is also a past history of migraine. One interesting point is the fact that there was a marked degree of impotence during the few days' duration of the congested liver attacks. The patient appears to be psychologically normal. Opinions obtained as to treatment are varied, such as the use of testosterone, antuitrin S, and psychiatry. If an endocrinological investigation be indicated, what tests might be necessary?

REPLY.—This patient has had diabetes mellitus for seven years, and it is presumed that the condition is under adequate control. It is therefore unlikely that his impotence is due to it, although it is well recognized that diabetes can be a cause, and stabilization does not always lead to an increase in potency. Once stabilization has been achieved, however, it is probable that impotence developing later is unconnected with the diabetes. There is some evidence of this in this case, in that he suffered from impotence during his "liver attacks" before the onset of his diabetes. The large majority of cases with impotence owe their symptoms to psychological causes. This patient is said to be psychologically normal, but nevertheless gives a history of persistent masturbation, and is a migrainous subject, both of which can be regarded as in part neurotic manifestations. Also the liver attacks may well be related to his impotence by blunting psychological stimulation during a temporary depression of his general health.

It is possible that some atrophy of the testicles is developing, in which case testosterone therapy might prove useful, and it is suggested that injections of the propionate (25 to 50 mg. three times a week) be used as a therapeutic trial, and if successful, implantation of six 100 mg. tablets under the skin is carried out. This should prove effective for about six months, and testosterone will have no effect, good or bad, on his carbohydrate metabolism.

Endocrine investigations would probably not add much to the understanding of the case, but of them, testicular biopsy would be most likely to be informative. If it showed any abnormality the estimation of the urinary follicular stimulating hormone and the 17-ketosteroids might help in deciding whether the defect was primarily pituitary or gonadal in origin. In brief, it is thought that this man's impotence is probably unconnected with his diabetes and is due to psychological rather than to physical

causes. It is suggested that testosterone be given a therapeutic trial and that this constitutes the only necessary investigation. If it proves ineffective, psychotherapy could be considered, but an enlightened discussion with the general practitioner should be given priority over a more highly specialized approach.

JOHN S. RICHARDSON, M.V.O., M.D., F.R.C.P.

Administration of Vitamins to Members of Police Force

QUERY.—Could you tell me whether there is justification for advising the routine administration of vitamins A and D to members of a Police Force as a prophylactic measure to increase vitality and resistance to infection? For some years one capsule of a proprietary preparation has been issued in this area as a routine.

REPLY.—Considerable work has been done upon this problem (e.g. Bransby, Hunter, Magee and Milligan, *British Medical Journal*, 1944, i, 447; 1946, i, 193). In the experiments described in these articles 214 adult men and about 4000 children were fed vitamins in capsule form containing the adult daily requirements of vitamin A, thiamin, niacin, riboflavin, ascorbic acid, and calciferol for from six to twelve months. Tests showed that the extra vitamins had no discernible effects on health, incidence of illness, rate of growth of children, physical efficiency, endurance, or industrial output. It was therefore reasonable to conclude from these findings that the national diet at that time (1941-44) contained a sufficiency of these vitamins at any rate for school children, and for a group of industrial workers, whose employment was extremely strenuous and exhausting. The diet has not altered in recent years in any way likely to affect these conclusions.

A study carried out by the Ministry of Health on members of the Metropolitan Police Force in 1948 suggests that the conclusions in regard to industrial workers applies equally to this body of men.

W. T. C. BERRY, M.B.

Doctor Dover

DR. SUGARÉ writes: "I was very interested in the article on "Diaphoretics", by Professor K. Douglas Wilkinson, in the April issue of *The Practitioner* (p.336). I have been sufficiently long in general practice to have used, and still use, some of the preparations mentioned. I refer in particular to Dover's powder. In this connexion may I draw your readers' attention to the interesting historical article in *Country Life*, April 8, 1949, entitled "The Daring Doctor Dover", by Aytoun Ellis. When the ship called "The Duke", of which Dr. Dover

Hurst's tubes, are fairly thick-walled rubber tubes, sealed at each end and half filled with mercury; the weight of the column of mercury forces the cardiac sphincter open. It is advisable to start with a small bougie, 24 gauge, which should be lubricated with glycerin or liquid paraffin. When passing a bougie for the first time, it is better to pass it with the patient behind the X-ray screen, so that the position of the tube can be checked radiologically by administration of sips of the barium paste. Once the patient has mastered the art of swallowing a bougie, he is soon able to tell when the tube has passed through the cardiac sphincter. The bougie should be passed before each meal and kept in position for fifteen to twenty minutes. Many patients find that an octyl nitrite inhaler or a trinitrin tablet administered just before the bougie is swallowed makes the procedure somewhat easier. The size of the bougie used should be increased by working up to a 30 or 34 gauge.

When the bougie has been passed regularly for two or three months it is often possible to reduce the frequency of this procedure to twice daily, preferably in the evening and on rising in the morning, and later to once daily, and then even weekly. During the initial stages of treatment, diet should be semi-solid, and food must, of course, be thoroughly masticated. The Sippy diet is seldom necessary except if there is œsophagitis as a result of prolonged stagnation of food in the lower œsophagus. Phenobarbitone may be used in the initial stages of treatment for nervous or apprehensive patients, but should not be continued once the patient is practised in the art of passing a bougie.

R. GWYN EVANS, M.B.E., M.D., M.R.C.P.

NOTES AND QUERIES

Postponement of Menstrual Bleeding

QUERY.—I should be obliged if you could give me information on the following problem: How best can the normal menstrual cycle be postponed for a few days in a normal healthy married woman, and what measures can be taken to procure this effect? Is it possible to obtain postponement by a method of treatment which can be given in the luteal, i.e. post-ovulatory, phase?, and if so, which drugs should be taken, and can they be administered by mouth? I am often questioned on this subject by Service personnel going on leave.

REPLY.—The normal menstrual cycle may be interfered with in the following ways:

(1) Large doses of œstrogen given as early as possible in the cycle will induce an œstrogen withdrawal bleeding within three or four days of discontinuing administration. For instance, 3 mg. of stilbœstrol given daily by mouth, beginning on the first to about the fifth day of the cycle will inhibit ovulation and produce a withdrawal bleeding three or four days after a ten to fourteen day course of treatment. This withdrawal bleeding, in the absence of further endocrine therapy, should be followed by normal cycles.

(2) After about the fifth day of the cycle, and certainly after the tenth day, it is not easy to influence the normal course of events. (a) Large doses of androgen, e.g. 50 mg. of methyl testo-

sterone daily, given until the day to which it is desired to postpone bleeding may produce the desired effect, but androgens have a marked individual variation in effectiveness, and one could not guarantee that they would achieve the result aimed at, especially if they were administered during the luteal phase of the cycle. (b) Very large doses of chorionic gonadotrophin, provided they are administered early in the luteal phase, might prolong this phase. They would have to be given intramuscularly in doses of, say, 5000 I.U. every second day until after the time at which it was desired to postpone bleeding.

Thus it is not at all easy to change the pattern of any particular normal, ovulatory, menstrual cycle unless there is an opportunity of doing so at the very beginning of the cycle.

PETER BISHOP, D.M.

Impotence and Diabetes

QUERY.—A male patient, aged thirty-four years, a diabetic on insulin for seven years, now complains of impotence for nine months accompanied by frequent attacks of testicular pains with very slight tenderness of the testicles. The pains have disappeared now that the impotence has asserted itself. Further, the patient gives a history of persistent masturbation dating back to puberty. Matrimonial life is happy, with two children. Previous to the diabetic state being

of *Clinical Pathology*, April 1949, 19, 372). The bis salt was used in dosage of 0.1 mg. per kg. of body weight, 1 mg. of the dry salt being dissolved in 1 ml. of normal saline. The total volume injected varied from 5 to 10 ml., and the injection was made intravenously. Four daily injections constituted a course of treatment. Thirteen of the patients were X-ray-resistant, and of these, two showed no improvement with nitrogen mustard, three showed minimal improvement, five had remissions for less than six weeks, and three had remissions for more than six weeks. Of the 14 patients who were still X-ray sensitive, four showed minimal improvement, five had remissions of less than six weeks' duration, and five had remissions of more than six weeks. The remaining 16 patients had no X-ray treatment, and of these, three showed minimal improvement, four had remissions for less than six weeks and nine had remissions for more than six weeks. In three cases treatment had to be stopped because of severe and sudden depression of one or more blood elements. The most striking clinical response to treatment was decrease in the size of superficial glands. The spleen decreased in size in most cases, pain was usually relieved and fever reduced. It is concluded that in the treatment of Hodgkin's disease nitrogen mustard is indicated: (1) when the lesions are generalized; (2) when the condition is X-ray resistant; (3) in the presence of generalized symptoms, e.g. fever and itching. It is emphasized that this is a form of treatment which should only be given in hospital.

Bismuth and Goitre

ACCORDING to Manuel Villaverde (*Journal of Clinical Endocrinology*, May 1949, 9, 462), bismuth salts are of value in the treatment of simple goitre, by causing a reduction in the size of the gland. They have no effect upon the function of the gland and are therefore of no value in the treatment of thyrotoxicosis. In two out of three cases of hyperthyroidism controlled by thiouracil, however, the subsequent administration of bismuth salts was followed by a reduction to normal in the size of the gland. In the third case there was no effect. The two salts of bismuth that were used were the subsalicylate (0.13 g. of bismuth per ml.) and the heptadienecarbonate (0.045 g. of bismuth per ml.). Both were given intramuscularly: the subsalicylate in doses of 1 ml. weekly or 0.5 ml. twice weekly, and the heptadienecarbonate in doses of 0.5 ml. twice weekly, to a total of 20 injections. After an interval of two to four weeks a second series of 20 injections was given if necessary, and in a few cases this was followed after a similar interval by a third series of in-

jections. The results were as follows: of ten patients with diffuse simple goitre, five showed "great improvement", two showed "slight improvement", and there was no response in three patients. Of six cases of nodular goitre, three showed "great improvement", one showed slight improvement and two failed to improve. In the majority of patients two series of injections were required. Two patients had three series of injections and both showed "great improvement".

Comparison of the Newer Antibiotics in Peritonitis

G. H. YEAGER, C. H. INGRAM and W. A. HOLBROOK (*Annals of Surgery*, June 1949, 129, 797) record the results of a comparative trial of streptomycin, aureomycin and chloromycetin in experimental peritonitis, and also in four clinical cases. For the experimental investigation, peritonitis was produced in adult dogs by ligating the appendix and crushing the distal end. Ten animals were used as controls: the recovery rate in this group was only 20 per cent. Ten were treated with streptomycin: starting twenty-four hours after operation, 75 mg. were administered intramuscularly, six-hourly, for eight days: the recovery rate was 60 per cent. Ten dogs received aureomycin, starting twenty-four hours after operation with 100 mg. by mouth, four times daily, for eight days: the recovery rate was 90 per cent. One further dog was treated with chloromycetin and recovered; a further series is to be treated with this drug. In the four clinical cases the infecting organism was *Escherichia coli*. In one case of infection of the urinary tract followed by generalized peritonitis the patient was first given streptomycin, 250,000 units three-hourly, but failed to improve. He was then given sulphadiazine, 3 g. intravenously daily, and aureomycin, 300 mg. intramuscularly every six hours. After five days, sulphadiazine was discontinued and aureomycin continued alone. Before the institution of aureomycin therapy the patient had been comatose, but within twenty-four hours he showed marked response to the drug. Aureomycin was discontinued on the twelfth day; *Proteus vulgaris* was cultured from the abdominal wound. Several days later the discharge from the wound increased and *Escherichia coli* was again cultured. Aureomycin was resumed with immediate improvement. The patient was discharged on the thirtieth hospital day, twenty-five days after the institution of aureomycin therapy. Of the other three cases, one was an infection of the urinary tract and peritonitis, and two were gangrenous appendices followed by peritonitis. All re-

was second captain, reached Juan Fernandez, an island which they believed to be uninhabited, the sailors were quartered in a church but were unable to sleep owing to the "appalling stench". None of them knew that the dreaded bubonic plague had stricken the nearby city of Guayaquil in Ecuador, and the noxious smell arose from the fact that many victims had just been buried. Within two days of putting out to sea, 180 of the crew went down with the disease. Dr.

Dover's treatment was leeching and the administration of copious doses of sulphuric acid. "Miraculously only eight of the crew died". It is said that this treatment was patterned on that of the famous Dr. Sydenham, from whom Dr. Dover had received his early training in London, where later he became his assistant and was cured by him of smallpox, being made to "take twelve bottles of small beer, acidulated with spirits of vitriol, every twenty-four hours".

PRACTICAL NOTES

Diethylstilbæstrol in Mumps Orchitis

THE use of diethylstilbæstrol as a prophylactic and also as a therapeutic measure in mumps orchitis is recorded by A. L. Hoyne, J. H. Diamond and J. R. Christian (*Journal of the American Medical Association*, June 25, 1949, 140, 662). Thirty-nine adult male patients were admitted to hospital with mumps; of these nineteen had orchitis of varying degrees of severity. The 19 patients with orchitis were given diethylstilbæstrol immediately on admission, in dosage of 5 mg., followed by 5 mg. every morning until the orchitis subsided. A lower dosage was used in the milder cases. The response in some cases was dramatic: decrease in pain and tenderness and a lessening of the patient's general toxicity occurred within twenty-four hours. In each case response was good and there was uneventful recovery. The average duration of treatment was 4.73 days, and of hospitalization 5.98 days. The 20 patients admitted without orchitis were given diethylstilbæstrol as a prophylactic: 1 mg. on admission and each morning until the parotitis subsided. Of the 20 patients, 13 were treated with this dosage: 3 developed unilateral orchitis. The dosage was then increased to 2 mg., and the remaining 7 patients were treated by this method: none developed orchitis. In conclusion it is stated: "The simplicity of oral administration and the lack of toxic effects, together with the dramatic clinical results, make diethylstilbæstrol the treatment of choice as a prophylactic and also as a therapeutic agent for mumps orchitis".

Contact Lenses

AN analysis of the answers to a questionnaire submitted to 875 wearers of contact lenses is given by A. G. Cross (*British Journal of Ophthalmology*, July 1949, 33, 421). In more than half the cases contact lenses were employed for myopia, especially in young patients; other conditions were mustard-gas keratitis, keratoconus and aphakia. The largest age-group was

twenty to thirty years; few contact lenses were ordered under the age of eighteen or over sixty. The tolerance figures show that 33 per cent. had given up wearing their lenses; the highest figure for those who persisted with the contact lenses was in the age-group over fifty, which included a number of males with mustard-gas keratitis. About one-third of the 875 patients could wear their lenses for eight hours or more; only 16 per cent. could wear them for less than four hours. The over fifty age-group again showed the highest figure for those wearing contact lenses for eight hours or more. Fewer patients with keratoconus and myopia had given up wearing their lenses than those who were purely myopic; but the percentage of aphakic patients still wearing their contact lenses was even lower than for the myopes. Of the total continuing to use contact lenses, 39 per cent. put them into the eye dry; of those who used fluid, 73 per cent. used normal saline; the remainder used 2 or 2½ per cent. sodium bicarbonate solution, cold or warm water, distilled water, borie acid solution, "optrex", buffer solutions, and a few, saliva. Reasons for removing the contact lenses included: (1) veiling, blurring, fading vision or mist around lights, 39 per cent.; (2) pain, irritation, smarting, discomfort and watering, 30 per cent.; (3) cleaning, removing eyelashes, and renewing lotion, 18 per cent. Only about 20 per cent. of the entire group wearing contact lenses did not suffer at times from bubbles; these were not found to be a hindrance, and veiling appeared to be less marked when a bubble was present. It is stated: "Men have defaulted more frequently than women, possibly because of the greater determination of the latter to succeed for cosmetic reasons".

Nitrogen Mustard in the Treatment of Hodgkin's Disease

THE results of the use of nitrogen mustard in 43 patients with Hodgkin's disease are reported by L. A. Erf and R. D. Bauer (*American Journal*

each month for serological tests and physical examination. Serological tests were also carried out on mother and child at delivery, and thereafter monthly for six months, then every two or three months. There were four foetal deaths, two probably due to syphilis. Six patients went into premature labour during the course of penicillin therapy, and two of these children were born with congenital syphilis. One patient had a serological relapse before delivery and gave birth to a syphilitic child. Thirty-two children born of the women in the series are living and non-syphilitic. Relapse of the syphilitic condition occurred in five of the thirty-nine mothers.

Papaverine in the Treatment of Pruritus

L. ROUQUES (*Presse Médicale*, July 16, 1949, 57, 671) discusses the use of papaverine in the treatment of pruritus by R. N. Corti and C. F. Guillot (*La Prensa Médica Argentina*, 1949, 36, 883). These authors treated a series of fifteen cases: three of senile pruritus, four of Besnier's pruritic eczema, six of microbial eczema, and two cases of psoriasis. The drug (100 mg. of papaverine hydrochloride in 2 ml. of distilled water) was given by intravenous or intramuscular injection, one injection at 11 a.m. and a second at 5 p.m., the total number of injections varying from 10 to 30. Twelve of the patients were completely cured of their pruritus; three showed only moderate improvement (these three cases were the 2 of psoriasis and 1 of eczematic prurigo). The authors considered that the intramuscular route was preferable; intravenous injection caused a sharp vasodilatation, with a feeling of heat, redness of the face, and malaise, which disappeared in a few minutes. Intravenous injection also caused a tendency to somnolence, and in one case tachycardia, tachypnoea and temporary loss of consciousness occurred. Using the intramuscular route there were no secondary side-effects: although the calming effect on the pruritus was slower by this route than by intravenous injection (two to three hours instead of a few minutes) the effect was more durable (six to seven hours instead of a quarter of an hour). In those cases in which the pruritus was predominantly nocturnal one intramuscular injection at 7 p.m. proved sufficient.

Dietetic Regime for Hypertension and Cardiac Insufficiency

In view of the return to favour in America of Kempner's dietetic regime for hypertension and

cardiac insufficiency, a regime composed largely of rice and fruit, rich in glucides but with low fat, nitrogen and chloride content, R. Reverdin and A. Mutrux (*Médecine et Hygiène*, January 1, 1949) evolved a modification adapted to European taste and facilities. Both diets are discussed by A. Ravina (*Presse Médicale*, June 25, 1949, 57, 607). The American regime is as follows:—

Breakfast: 60-90 g. of rice (boiled, steamed or baked with neither fat, milk nor salt) with milk or honey
two-thirds of a glass of prune juice
1 baked apple
1 grapefruit
10 a.m.: half a glass of orange juice
1 orange and some grapes
Lunch: rice, as for breakfast
half a glass of orange juice
1 banana with 6 slices of apple
1 slice of pineapple, cherry, and dried raisins
3 p.m.: half a glass of orange juice
1 apple and dried peaches
Dinner: rice (as for other meals)
two-thirds of a glass of orange juice
plate of fruit
9 p.m.: half a glass of orange juice

The sugar must be refined white. Sweets and jellies composed exclusively of sugar and fruit without colouring or chemical content. Vitamin B complex.

The regime is followed for three months, with addition, after fall of the blood pressure, of a cup of tea or sugared coffee, and half a spoonful of cooked vegetables daily, and one egg weekly. Then after fifteen days to a month, 120 g. of poultry or white meat, cooked without salt, thrice weekly, and 2 eggs per week. On the seventeenth day boiled vegetables and two slices of bread without salt are added, and at the end of six weeks, if the pressure remains down, 125 g. of lean meat or poultry four times weekly, 3 eggs weekly, and boiled potatoes and vegetables (non-leguminous) daily.

The French modification is:—

Midday: rice 75 g., apples 325 g., sugar 30 g.
Evening: rice 75 g., apples 200 g., flaked cereals 20 g.,
sugar 25 g., condensed milk 20 g.

In addition, the patient eats during the day 2 bananas, 3 oranges, 3 to 4 apples, and 200 g. of bread without salt.

The regime differs from Kempner's in that it supplies 2,290 calories instead of 2000 calories, and includes only 150 g. of rice, but the principle of dechlorination is strictly adhered to. Additions are: dechlorinated powdered milk and other ingredients to thicken the rice; pure flour for puddings or creams made without milk; and the addition of tomatoes, onions, leeks, celery, mushrooms or bay leaves to the unsugared rice; or the rice may be eaten in the form of rizottos prepared with paraffin oil. It is stated that in spite of such culinary embellishments the diet is difficult to tolerate, but the results obtained, as reported by American authors, fully compensate for the sacrifice entailed in carrying out the monotonous regime.

sponded to aureomycin therapy after sulphathalidine and streptomycin, in the urinary tract infection case, and penicillin, in the cases of appendical peritonitis, had failed to effect a cure.

Treatment of Bee Stings

"BECAUSE of the probable presence of histamine in bee venom and because of the close resemblance of the symptoms to those induced by histamine", W. T. Strauss (*Journal of the American Medical Association*, June 18, 1949, 140, 603) investigated the effect of an anti-histamine drug in the treatment of stings. The preparation used was theophorin, and it was applied in the form of a 5 per cent. ointment. In eight cases of bee stings and ant bites the ointment was applied liberally at the site as soon as possible, usually within a few minutes after the injury. The ointment was rubbed gently into the site. "In every instance the intense pain and stinging sensation was relieved within one or two minutes". In most cases no local swelling occurred, and there were no toxic effects from the use of the drug. Details are given of one case: a boy aged five years who walked into a swarm of bees and was stung seven times. Theophorin ointment was applied within a few minutes and "the cries of the child subsided in less than one minute, and he stated that all of the pain had disappeared". It is suggested that such an ointment may also be of value in the treatment of the stings of hornets, wasps and mosquitoes.

Gynæcomastia and Cirrhosis of the Liver

Two cases of gynæcomastia complicating cirrhosis of the liver are reported by J. Mithoefer and W. B. Bean (*Surgery*, June 1949, 25, 911). Both were elderly males and in both the gynæcomastia was unilateral. Hair distribution and the genitalia were normal in both. On removal of the breasts the histological changes were those "generally recognized as resulting from oestrogenic activity", e.g.: "(1) epithelial proliferation resulting in the piling up of cells and their projection into the lumen of the ducts in the form of pseudo-papillæ; (2) multiplication of ducts with an increase in diameter, occurrence of tortuosity and formation of branches; (3) change in the character of the periductal connective tissue . . . (4) the appearance of relatively large mononuclear cells . . ." In neither case was there any evidence of malignancy. Having seen fourteen such cases during the last year, the authors feel that "the finding of gynæcomastia should direct attention to the possibility of chronic disease of the liver", an association that was first commented on in 1926 by Silvestrini.

A Buttermilk Substitute for Infant Feeding

THE formula of a buttermilk substitute, which is stated to be sterile, of better flavour and more constant acidity than buttermilk, and easy to make in the average home, is given by R. H. Crisp (*Medical Journal of Australia*, May 28 1949, 36, 717). The ingredients are as follows:—evaporated milk ("ideal"), 6 ounces (170 ml.); water, 24 ounces (680 ml.); milk protein powder ("protosol"), $\frac{1}{2}$ an ounce (15 g.); lactose syrup, $\frac{1}{4}$ of an ounce (21 ml.). The food is prepared by dissolving the protosol in hot boiled water at night, covering, and allowing to cool until morning, when the cold "ideal" milk is added. The lactose syrup is then slowly stirred in. This makes 30 ounces (about 1 litre) of the food, which contains: protein 3.2 per cent.; fat 1.6 per cent.; carbohydrate 4.5 per cent.; mineral 0.47 per cent. The acidity is pH 4.88, and the caloric value 14 calories per ounce. Extra carbohydrates, such as lactose, cane sugar, dextrimaltose, or cereals can be added as required; in cases of acute upset this addition should be gradual, after the acute phase has passed. Extra vitamins, also, are added as a routine, for example, "pentavite" 15 drops, or one to two ounces of orange juice. It is stated that "B.M.S." can be regarded as a temporary medicinal food, but if its limitations are borne in mind it may form the basis of feeding for a long period. It has been used successfully in the following types of case:—(1) In the treatment of new-born and premature infants; (2) in acute dyspepsia; (3) in diarrhoea, acute or chronic; (4) in malnutrition, dystrophy, and chronic fat dyspepsia; (5) in milk allergy; (6) in those cases in which a food of high protein and low fat content is desirable, e.g. congenital steatorrhoea with pancreatic defect, coeliac disease, liver disorders, and nephrosis.

Crystalline Penicillin G in Syphilis in Pregnancy

A REPORT of the results in a series of thirty-nine pregnant women treated for syphilis with crystalline penicillin G is given by J. B. Cross, J. R. McCain, and A. Heyman (*American Journal of Obstetrics and Gynecology*, March 1949, 57, 461). The majority of the patients were treated late in the course of pregnancy: twenty between the sixteenth and thirty-second weeks; fourteen after the thirty-second week; five before the sixteenth week. The dosage employed was 80,000 units of crystalline penicillin G, three-hourly for sixty injections during seven and a half days. No additional treatment was given. After completion of the course of treatment the patients were instructed to return

volume. It is written for a wide range of readers—the practitioner in a hurry for specific data, the clinician desiring detailed information for the investigation of a given problem and the laboratory worker in search of technical data for immediate practical application. In attempting to meet such diversified needs, the author's main objective has been to bring out as clearly as possible the special considerations and technical data made necessary by the physiological peculiarities of the growing child: he has included all physiological functions which it may be desirable to test in children, even psychological testing, but he has omitted investigations of a morphological nature such as routine procedures of urine, blood and stool examination. This book is the answer to many a harassed worker's prayer for easier accessibility of all relevant technical knowledge.

Anæsthetics for Medical Students. BY GORDON OSTLER, M.B., B.Chir., D.A. London: J. & A. Churchill Ltd., 1949. Pp. vii and 108. Price 7s. 6d.

SURELY the production of this book, the first on anæsthesia written primarily for medical students, is a sign of the times. It is a concise and elementary manual of facts which should enable would-be anæsthetists to understand the principles and avoid the common pitfalls of anæsthesia.

Fundamentals of Pulmonary Tuberculosis and its Complications. EDITED BY EDWARD W. HAYES, M.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications, 1949. Pp. x and 470. Figures 182 and 4 colour plates. Price 50s.

This book, sponsored by the American College of Chest Physicians, consists of twenty-six monographs from twenty-seven well-known chest physicians and teachers. In the foreword, Dr. Myers says the book is intended for students and graduates of medicine so that they may study and have readily available the most modern facts and medical points of view on all phases of tuberculosis. It is certainly true that the book is comprehensive. It is doubtful, however, whether all the essential statements given are really required by the average student and postgraduate; it is rather a half-way house between the knowledge necessary for the professor of medicine who deals with tuberculosis as one of his subjects and the postgraduate who wishes to take up tuberculosis as a specialty. In other words, it is unbalanced. The first five chapters are very good. Chapter VI, on the bacteriological infection and pathology of tuberculosis, is over-

specialized, as is Chapter XV, on major surgical procedures, and chapter XXI, on genitourinary tuberculosis, whereas chapter IX on the rôle of the X-ray errs in the other direction, for it could hardly be more general. Some chapters, however, like the early ones of Dr. Myers, are classics by the rules laid down in the introduction; this particularly applies to chapter XVIII, on the public health aspects of tuberculosis control, by H. E. Hilleboe.

NEW EDITIONS

Notes on Infant Feeding, by G. B. Fleming, M.D., F.R.C.P., F.R.F.P.S., and Stanley Graham, M.D., F.R.C.P.Ed., F.R.F.P.S., in its third edition (E. & S. Livingstone Ltd., 3s) was primarily compiled for the use of students at the University of Glasgow, and embodies the principles of infant feeding followed at the Royal Hospital for Sick Children, Yorkhill. In their preface the authors state: "The feeding of the infant should not be left to the nurse. The physician should be able to give precise instructions." In this little book practitioners will find valuable information on breast and artificial feeding, both for normal and abnormal infants.

A NEW chapter on anomalies of convergence has been added to *The Practice of Refraction*, by Sir Stewart Duke-Elder, M.C.V.O., M.D., D.Sc., F.R.C.S., in its fifth edition (J. & A. Churchill Ltd., 18s), as well as sections dealing with streak retinoscopy and velonioskiascopy. Practitioners will find much useful information in the chapters on muscular imbalance, myopia, and eye strain. In the chapter on the making and fitting of spectacles the section on contact lenses has been enlarged.

A Practice of Orthopædic Surgery, by T. P. McMurray, C.B.E., M.B., M.Ch., F.R.C.S.Ed., in its third edition (Edward Arnold & Co., 30s.) has been subjected to revision in several sections. There is a useful chapter on acute anterior poliomyelitis, in which diagnosis and general and local treatment are discussed in detail. This is a well-illustrated and practical presentation of orthopædic surgery.

The Theory and Practice of Massage and Medical Gymnastics, by Beatrice M. Goodall-Copestake, in its seventh edition (H. K. Lewis & Co. Ltd., 21s) contains a new chapter on "ward exercises" for the use of patients confined to bed. The chapter on war injuries has been replaced by one dealing with rehabilitation.

Plaster of Paris Technique, by Edwin O. Geckeler, M.D., in its second edition (Baillière, Tindall & Cox, 16s 6d) is a valuable contribution to plaster of Paris technique, and the many well-produced illustrations, 236 in all, are a practical aid to its practice.

REVIEWS OF BOOKS

Blood Transfusion. BY ELMER L. DEGOWIN, M.D., ROBERT C. HARDIN, M.D., and JOHN B. ELSEVER, M.D. Philadelphia and London: W. B. Saunders Company, 1949. Pp. xii and 587. Figures 200. Price 45s.

Blood Transfusion. EDITED BY GEOFFREY KEYNES, M.D., F.R.C.S. Bristol: John Wright & Sons Ltd., 1949. Pp. xii and 574. Figures 109. Price 52s. 6d.

THE avowed aim of both groups of authors, three American and eight English, is to present a comprehensive survey of the whole field of blood transfusion work. The Americans succeed in some measure, and in so doing they have produced a highly technical opus. In the clinical section useful advice is proffered as to the relative merits of fresh blood, stored blood, concentrated cells and plasma in the treatment of disease, but their usage of the term "shock" covers a wider classification than is common in this country. The section on laboratory technique is embellished with a large number of drawings of the apparatus required for each stage of each test, which, whilst impressing the memory of some workers, may prove merely irritating to others. Wiener's nomenclature for the various Rh subgroups is used throughout a stumbling block for the non-specialist in this country who is only familiar with Fisher's symbols. The subject is rounded off by a detailed description of the processing of whole blood and its derivatives, and advice on the organization of a hospital blood bank. There must be few people to whom this book will appeal in its entirety, although interested clinicians and technicians will both learn something from a study of American methods.

The British version of the same subject, although not so weighed down by technical description, appears eminently more practical. It is a pity, however, that so much space has been devoted to description of outmoded methods and apparatus which, whilst proving satisfactory before and during the war, must now have been almost entirely superseded by the standard apparatus of the National Blood Transfusion Service. Naturally, with a work in which so many authors have combined, the chapters are not all of equal merit. The history section is interesting, the description of transfusion technique is adequate when disentangled, and the portion dealing with the indications for transfusion will be found to be most helpful.

Each of these books has, in its own way, achieved its purpose and, although the price may be prohibitive to the non-specialist, either

would be a valuable acquisition for pathology laboratories and hospitals where intravenous therapy is undertaken.

Sir William Gowers 1845-1915. MACDONALD CRITCHLEY, M.D., F.R.C. London: William Heinemann (Medical Books) Ltd, 1949. Pp. 118. Illustrated. Price 17s. 6d.

EVERY medical student has heard of Gowers' tract and Gowers's mixture, but few of them, of their present teachers, know anything of the brilliant clinician whose name is thus perpetuated in the annals of medicine. In this "biographical appreciation", published in limited edition, Dr. Macdonald Critchley has done his best to remedy this deficiency. The task has been a particularly difficult one because of the lack of material. Sir William was never very forthcoming, so that his colleagues and students never came to know him well. Nevertheless he was a good correspondent. In spite of the difficulties Dr. Critchley has succeeded in presenting a convincing portrait of his subject and his labour of love will be appreciated by those who are interested in the great school of English neurology. Gowers was a curiously reticent personality. In spite of his "superlative gift at the bedside" he never acquired a fashionable practice, nor did he ever attain high office in his own College. Academic honours were seldom his, but he was a Fellow of the Royal Society, and many foreign societies appointed him to honorary membership. On the other hand, in one of the most brilliant periods of English neurology he held his own with the ablest colleagues and left behind him a record which has seldom been equalled. Fortunately his writings were extensive, and one of the valuable features of this brief biography is the inclusion of a complete bibliography of his published works.

Diagnostic Tests for Infants and Children. BY H. BEHRENDT, M.D. New York and London: Interscience Publishers Ltd, 1949. Pp. xvii and 529. Figures 41. Price 57s.

THIS comprehensive book of reference on the principles, practice and interpretation of clinical and laboratory procedures in infancy and childhood will rapidly become an indispensable volume on the shelves of all engaged in paediatric practice. It is a great convenience to have, for the first time, all the technical information of current value in paediatrics collected together in one

THE PRACTITIONER

No. 976

OCTOBER 1949

Volume 163

ADVANCES IN MEDICINE

By CLIFFORD WILSON, D.M., M.R.C.P.

Professor of Medicine, University of London; Director, Medical Unit, London Hospital.

"The principal defect on the part of physic proceeds, not from a scarcity of medicines to answer particular intentions, but from a want of knowing the intentions to be answered".—Thomas Sydenham.

THE "Father of English Medicine" was concerned with the "medicines which purge, vomit, or sweat, or cool". Therapeutic techniques are to-day both more varied and more specific; but the main advances in medical treatment during the past year have been elaborate variations on Sydenham's theme. Much effort, thought and planning have been devoted to the assessment of new remedies and, as the section headings of this number bear ample witness, the alignment of the science and art of therapeutics has become increasingly more complex and specialized.

New remedies for the most part pass through three stages: discovery, assessment, and rationalization, this paradoxical order deriving largely from the fact that chance is often kinder to the experimenter than logic, so that powerful new drugs are apt to be discovered before their mode of action is clear. The urgency to heal cannot wait on the complete understanding of either the remedy or the malady, so that in the subsequent process of rationalization the fundamental nature of a disease and of its cause is often revealed or clarified. In this manner, liver was found to cure pernicious anæmia, but the search for the essential factor in liver therapy which has been carried on over the past twenty years has only recently achieved success; a new light has thereby been thrown on the causation of the "idiopathic anæmia" which Addison described 100 years ago.

An account of recent advances in medical treatment must therefore include all these features. There are the new discoveries—a rich and continuing by-product of modern developments in the exact sciences; but their present value is measured in hope and inspiration. The more practical contributions result from the trial and assessment of recent discoveries, the definition of risks and limitations, and of the exact conditions for successful results. Finally, there are the additions to fundamental knowledge which derive from the investigations of therapeutic activity, and form the basis for the next advance.

NOTES AND PREPARATIONS

NEW PREPARATIONS

"CRESATIN" metaercsylaectate (Sulzberger) is stated to be a powerful antiseptic and fungicide with penetrating and analgesic properties and a prolonged action. Its use is indicated in the treatment of infections of the ear, nose and throat, ringworm of the feet, and infected tooth sockets and root canals. (Sharp & Dohme Ltd., Hoddesdon, Herts.)

DISECRON is a compound solution of œstradiol monobenzoate 2.5 mg., and progesterone 12.5 mg., in 1 ml. of ethyl oleate, for intramuscular injection in the treatment of secondary amenorrhœa by a simplified technique of only two injections monthly. ETHIDOL (ethinyl œstradiol), a derivative of the natural œstrogenic hormone α -œstradiol, is stated to be relatively non-toxic and highly active by the oral route. (British Schering Ltd., 167-169 Great Portland Street, London, W.1.)

IQUINOL (5:7-diiodo-8-hydroxyquinoline), stated to be a tasteless and non-toxic iodine compound containing 63.9 per cent. iodine, has been prepared for the prophylaxis and treatment of amœbiasis and trichomoniasis (Genatosan Ltd., Loughborough, Leics.)

METHIONINE B.D.H. is the amino-acid, γ -methylthiol- α -aminobutyric acid, a substance claimed to prevent and arrest fatty degeneration of the liver. It is supplied in bottles of 50 and 250 sugar-coated tablets of 0.25 g. (British Drug Houses Ltd., Graham Street, London, N.1.)

TELEVISED EYE OPERATIONS AT ST. THOMAS'S

ON July 21, 1949, eye operations, including the use of diathermy for detached retina, were televised at St. Thomas's Hospital by a Mareoni Image Orthicon camera, which was mounted above the operating table, every detail being relayed to a nearby room, where surgeons and students saw the operations magnified six times on a 15" screen. It is of interest to note that it was from St. Thomas's that Signor Mareoni in May 1898 demonstrated his system of wireless communication to Members of Parliament on the other side of the river.

BRITISH RHEUMATIC ASSOCIATION

AN exhibition of aids, appliances and services for the rheumatic will be held at the Town Hall, Chelsea, from September 27-30, 1949. A two-day conference on the welfare of the rheumatic patient will take place concurrently. Tickets for the conference, price 10s., and full particulars can be obtained from the Secretary, 5 Tite Street, London, S.W.3.

MEDICAL FILMS

A FILM on *poliomyelitis* entitled "His Fighting Chance", with introduction by Michael Redgrave and a commentary by Mrs. Roosevelt, stresses the importance of early treatment and the encouraging results obtained thereby. It has been prepared by the Crown Film Unit for the Central Office of Information, and will shortly be available on free loan. The running time is 10 minutes. (Central Film Library, Imperial Institute, London, S.W.7.)

"*Thiopentone Sodium and its Use in Intravenous Anaesthesia*" (made in cooperation with the Department of Anaesthetics, Westminster Hospital): running time 38 minutes, and "*Medical Applications of Sulphonamides*": running time 34 minutes, both on 16 mm. and 35 mm. sound, are available to medical groups on request. (Documentary Film Unit, May & Baker Ltd., Dagenham, Essex.)

PUBLICATIONS

The P.J. Poisons Guide to the Pharmacy and Poisons Act 1933, the Poisons Rules, and the Pharmacy and Medicines Act 1941, with an extended Poisons List, has been fully revised in its fifth edition. (Pharmaceutical Press, Price 3s. 6d.; interleaved copies, 4s.)

The Nuffield Foundation. The fourth Report of England's biggest charity reviews the work accomplished during the past six years, and discusses future policy. (12-13 Mecklenburgh Square, London, W.C.1.)

The British Empire Cancer Campaign. The twenty-sixth Annual Report, edited by Sir Heneage Ogilvie, covers the work carried out during 1948. (11 Grosvenor Crescent, London, S.W.1.)

The British Red Cross Society. The Annual Report of the Society for 1948, with a Foreword by Lord Woolton, gives information on the manifold activities of the Red Cross during peace time. (14-15 Grosvenor Square, London, S.W.1, price 2s. 6d.)

EDITORIAL ANNOUNCEMENT

AN extra number of *The Practitioner* will be published in September, dealing with the National Health Service Act. This issue, containing over 100 pages of text, will present in sixteen chapters a reasoned review of the working of the Act in its first year. Subscribers will receive this number without extra cost. Additional copies can be purchased at 5s. each, post free.

The contents of the October iss number devoted to "Advances found on page lxxiv at the end of

in the future. In the interim, the effective adrenal cortical or pituitary hormones, or chemically similar therapeutically active substances, may well be synthesized.

The stages of assessment and rationalization of the new therapy are likely to be laborious and prolonged; only the imagination can reach out to the vistas of new knowledge which they may open up in the fields of endocrine function, infectious disease mechanisms, and psychosomatic relationships.

ANTIBIOTICS

The year has seen notable advances in antibiotic therapy. "Slow absorption" penicillin compounds have been introduced, reports have appeared on large-scale trial and assessment of penicillin in syphilis, and of streptomycin in tuberculous and non-tuberculous infections. New antibiotics, particularly aureomycin and chloromycetin, have still further enlarged the range of infections which can be controlled by this form of therapy.

PENICILLIN

The most recent work has been directed to methods of prolonging the action of penicillin. The use of insoluble penicillin compounds to delay absorption now seems to be more practical and more effective than attempts to block penicillin excretion with such substances as caronamide. Penicillin forms insoluble salts with procaine and with aluminium, and the most promising results have been obtained by suspending procaine penicillin in a gel of aluminium stearate and peanut oil. A dose of 300,000 units of penicillin in this form will produce a therapeutic blood level for up to ninety-six hours (Thomas *et al.*, 1948). This preparation is now generally available and offers obvious advantages, for example, in the ambulatory treatment of syphilis, and in infants and young children. Wilson *et al.* (1949) obtained a therapeutic blood level for twenty-four hours or longer in babies after injection of 100,000 units. Whilst the maintenance of an "effective" blood level may be valuable, there is as yet no evidence that this is the most important factor in producing an effective concentration of penicillin in the tissues. Soluble sodium penicillin produces a higher initial peak level than the insoluble compounds, and controlled clinical trials must be carried out before these more convenient, and more expensive, preparations can be accepted as a fundamental advance in penicillin therapy.

The most interesting reports on clinical trials of penicillin during the past year describe the results of coordinated research on the *treatment of syphilis* in the United States. These results were recently outlined by Earle Moore (1949). Large numbers of patients have been treated and have been followed for several years.

The routine course of treatment consists of ten intramuscular injections of 0.6 mega unit of procaine penicillin in aluminium stearate-oil suspension, given daily or every second or third day. Follow-up observations over two years have been made on patients treated for early syphilis by this method and have indicated a failure rate of not more than 10 to 15 per cent. After a single dose of 600,000 units

RHEUMATOID ARTHRITIS AND THE ADRENAL CORTEX

The new discovery of the year and one which, by its implications, may rank among the greatest of medical science, is the relationship of the adrenal cortex to rheumatoid arthritis. Although little has yet been published, Hench and Kendall (1949) of the Mayo Clinic have in recent communications outlined the results of experiments which may in a few years' time provide a remedy for the most incapacitating of diseases. Starting from the observation that rheumatoid arthritis undergoes a striking remission during pregnancy, it was presumed that such remissions might be due to the increased circulation of adrenal cortical hormone. Various hormones isolated by Kendall were administered to patients with rheumatoid arthritis without success. Ultimately, compound E (17-hydroxy-11-dehydrocorticosterone), which has been termed "cortisone", was found to produce a striking remission in rheumatoid arthritis and also apparently in rheumatic fever. Fourteen cases have been treated and the results have been confirmed by independent trials in other clinics. The extract is effective only when given parenterally and its discontinuance is followed by prompt relapse. It appears therefore that, as in diabetes, treatment must take the form of repeated daily injections. Other effects of the drug include a sense of well-being amounting to euphoria, and increase in weight and appetite. A similar therapeutic effect has been obtained by administration of pituitary adrenocorticotrophic hormone (A.C.T.H.).

It must be appreciated that whilst the beneficial action of these substances in rheumatoid arthritis is both dramatic and unequivocal, the treatment is still in the experimental stage. The therapeutic dosage (100 mg. daily) is large, and smaller doses well within the range of pharmacological activity are without effect. The possibilities and dangers of harmful side-reactions need to be investigated fully, since both the adrenal cortical hormone and pituitary adrenotrophic hormone produce varied and important changes in electrolyte balance, protein and carbohydrate metabolism and sexual function. Owing to the minute quantities available these risks are not, however, immediate. Cortisone is manufactured by a complicated series of chemical processes involving some thirty stages from desoxycholic acid derived from ox-bile. Pituitary adrenocorticotrophic hormone is manufactured from hog's pituitary glands. Neither of these sources can in any circumstances provide enough active material for more than a limited clinical investigation. Of particular interest therefore is the recent announcement of a vegetable source of raw material for the preparation of cortisone. The seeds of the tropical vine, *Strophanthus sarmentosus*, which grows in East Africa and other equatorial regions, contain a glucoside which on hydrolysis yields *sarmentogenin*; this substance can be converted into cortisone by a somewhat shorter chain of reactions than is required when starting from desoxycholic acid. Unfortunately, the vine does not bear seed for five years after cultivation, but if propagation and culture can be satisfactorily carried out this source may provide large supplies of the drug

the same set of patients. Each patient should have at least four months in hospital before going to sanatorium. And the nursing is heavy. Indeed, for all concerned the treatment of tuberculous meningitis by streptomycin is a most exacting form of therapy".

One of the causes of failure is blockage of the subarachnoid space, either in the spinal theca or in the basal cisterns, particularly at the tentorial opening. Even in the absence of mechanical blockage, post-mortem examination of the brain in fatal cases often reveals a fibrinous exudate at the base of the brain which probably presents a barrier to the penetration of streptomycin. Cathie (1949) has described the preliminary results of combining streptomycin treatment with streptokinase in an attempt to overcome this barrier. Over a nine to twenty-three month period of observation, recovery occurred in 11 out of 19 cases given streptomycin-streptokinase therapy, compared with 3 out of 14 given streptomycin alone.

Controlled trials of streptomycin treatment in *acute progressive pulmonary tuberculosis* have been carried out in a number of centres under the direction of the Medical Research Council (1948). This pioneer experiment has shown the great importance of controlled cooperative therapeutic trials in assessing new remedies. Clinical and radiological improvement was significantly greater in treated than in untreated cases, but was usually apparent only in the early stages of treatment. Resistance to the drug develops after about six weeks' administration and most cases relapse within six months. It appears therefore that streptomycin alone provides a very imperfect answer to the problem of pulmonary tuberculosis. It may be used effectively in preparing for collapse therapy patients who would otherwise be too ill for surgical intervention. A serious social consequence of the development of streptomycin resistance is the danger of transmission of the infection to younger subjects, and the subsequent development of a tuberculous meningitis which is also streptomycin resistant.

Further work has recently been carried out in two different directions in an attempt to overcome this difficulty. For some time it has been known that certain chemical substances prevent the growth of tubercle bacilli *in vitro*. Of these, sulphetrone and *para*-aminosalicylic acid (P.A.S.) are the most effective. Clinical trials of streptomycin and P.A.S. therapy in pulmonary tuberculosis are at present being carried out, and there is reason to hope, from results both in America and in this country, that the problem of streptomycin resistance may be overcome. The alternative solution lies in the discovery of an antibiotic which does not produce resistant strains. Waksman, who discovered streptomycin, has now reported (1949) on a new antibiotic, "neomycin", which fulfils this condition and is less toxic than streptomycin. If clinical trials confirm the claims made for it, this discovery will solve many of the problems which now complicate the treatment of tuberculosis—although it may, of course, present new problems hitherto unsuspected.

(b) *Non-tuberculous infections*.—The chief penicillin-resistant infections which are sensitive to streptomycin are tularæmia, *Hæmophilus influenzae*

an effective blood level (0.03 unit per ml.) is maintained for five to seven days, and trials are being carried out on the treatment of early infection by a small number of doses at weekly intervals. The possibility is even envisaged of a cure being achieved by a single injection. No less striking are the effects of single prophylactic or abortive injections given after exposure to infection. In a controlled series of over 500 cases active infection showed a tenfold reduction in the treated group.

The social implications of this revolution in antisyphilitic therapy are obvious, if not inevitable. The wide scale of the investigation has been made possible by the high incidence of syphilis following the war. Granted a reasonable interval of uninterrupted application, the control of venereal infection would appear to be within reach for the first time.

STREPTOMYCIN

During the past year streptomycin has been made generally available by the Ministry of Health (1949) and is distributed through regional supply centres. It may be used in the treatment of certain specified tuberculous and non-tuberculous infections in which its value has been proved.

(a) *Tuberculous infection*.—Streptomycin treatment of tuberculous infections is discussed in detail in a later section (p. 510), and only some of the more general features will be mentioned here. Large numbers of patients have now been treated for *tuberculous meningitis*. Unfortunately the most satisfactory scheme of treatment has still to be worked out. Widely differing schemes have been used by different workers, often on such small groups of cases that the results are difficult to compare. The proportion of successful cases in a few centres has reached 50 per cent., but the usual figure is 20 to 30 per cent. Certain points require special emphasis:—

(1) Accuracy in diagnosis requires the closest attention. In view of the technically difficult and prolonged character of the treatment, and the possibility of serious toxic effects, it is essential that treatment should be undertaken in specially equipped centres, and then only after careful examination of the cerebrospinal fluid has been made and expert opinion has been consulted. The conditions which are likely to be confused with tuberculous meningitis include benign lymphocytic chorio-meningitis, virus meningo-encephalitis, poliomyelitis, acute disseminated sclerosis, and cerebral abscess. Mistaken diagnosis will expose such cases to protracted and even harmful therapy, or may cause a fatal delay in surgical intervention.

(2) In comparing different series longer courses of treatment, both intrathecal and intramuscular, produce the more successful results. Whilst no final conclusions have been reached, it appears that intramuscular streptomycin should be given for at least four, and probably for six months; intrathecal treatment should be continued for six to twelve weeks, and further courses may be needed. The situation is effectively assessed by Cairns and Taylor (1949) in the following words:—

“At least 50 per cent. of all cases treated are dying and there is thus ample room for improvement. In the present state of knowledge there is little to recommend the occasional treatment of isolated cases by individual doctors, and any hospital which establishes a centre must be prepared to have beds occupied for months on end by

a small series of cases of louse-borne typhus a favourable response was obtained. In the course of the clinical trials in scrub-typhus a number of patients with typhoid fever received the drug and showed a rapid improvement within twenty-four hours (Woodward *et al.*, 1948). A small and successful trial in this country has recently been reported by Bradley (1949).

The synthesis of chloromycetin holds out the hope of large-scale manufacture, whilst the possibility of effective oral administration provides a welcome alternative to the injection therapy of penicillin and streptomycin. These facilities carry with them an obvious danger—that of uncontrolled and indiscriminate prescription. The widespread use of penicillin, which has only been permissible by virtue of its relatively harmless toxic effects, emphasizes the urgency for much greater caution in the future. We are still ignorant of the minimal effective dosage of penicillin in the common infections, but extravagant doses are frequently employed both in treatment and prophylaxis, often without bacteriological diagnosis or indication. With the introduction of new antibiotics it is essential, in the interest of the patient no less than of economy, that bacteriological control should be regarded as a necessity rather than a luxury. Moreover, a micro-organism which is normally sensitive not infrequently develops a resistant strain, and it may be that following extensive use of antibiotics these strains are increasing in the bacterial population. Sensitivity tests should form an essential preliminary to treatment, and the laboratory services should be provided with special facilities for carrying them out.

VITAMIN B₁₂

The isolation of the active anti-anæmic principle in liver extracts has been delayed by the absence of simple and reliable tests of potency. The discovery that folic acid was an essential growth factor for *Lactobacillus lactis* Dorner provided a technique for laboratory assay, since anti-anæmic potency was found to parallel the growth requirements of the lactobacillus. The isolation of vitamin B₁₂ was thereby facilitated. During the past year further information has appeared on the clinical effects of its administration. Minute amounts of the vitamin have proved effective in pernicious anæmia, maximal reticulocyte responses and clinical remission following the injection of one microgramme daily. Subacute combined degeneration of the cord shows a response to vitamin B₁₂ which is comparable with that produced by liver therapy. Bethel (1948) identified a substance with similar action to B₁₂ in the stools of patients during a relapse of pernicious anæmia, and Callender *et al.* (1949) showed that injection of faecal extract from an untreated case of pernicious anæmia could produce a remission of the disease. The effectiveness of the vitamin when administered by mouth apparently depends upon the presence of gastric juice; hence the rôle, so long obscure, of Castle's "intrinsic factor" may be to promote the absorption of vitamin B₁₂.

It will be seen that major advances in treatment in such widely different conditions as infectious disease and pernicious anæmia have been facilitated

meningitis, penicillin-resistant staphylococcal infections, and infections of the urinary tract due to gram-negative bacilli, especially *Proteus*, *Ps. pyocyanea* and *B. coli*. A report from the Medical Research Council (Wilson, 1948) summarizes the results of clinical trials in 16 centres in this country. Influenzal meningitis is the most important of the conditions discussed and in a series of 34 cases the infection was controlled in 25 (74 per cent.), which justifies the conclusion that streptomycin alone is probably as effective as any other form of treatment at present available. Failures were almost entirely due to the development of bacterial resistance. As in the treatment of tuberculosis, attempts are at present being made to overcome this disadvantage by combined therapy, in this case with sulphonamides. In other forms of penicillin-resistant meningitis due to the organisms listed above, and in septicæmia of similar causation, streptomycin produces a rapid cure in the majority of cases. It is, however, almost useless in bacterial endocarditis. Streptomycin has also been widely used in the treatment of gram-negative urinary tract infection. A cure may rapidly be achieved with relatively small amounts of the drug (e.g. 3 g. daily, for three days) but in about half the cases studied, bacterial resistance developed. Underlying causes of urinary retention should be dealt with before streptomycin is employed.

AUREOMYCIN AND CHLOROMYCETIN

These new antibiotics have now received clinical trial in a number of infections which are unresponsive to penicillin or streptomycin therapy. Both drugs have a much wider "bacterial spectrum" than their predecessors and pilot investigations indicate that rickettsial diseases, including both louse-borne and mite-borne typhus, psittacosis, virus pneumonia and typhoid fever, may now be found responsive to antibiotic therapy.

Aureomycin is potent only in acid solution (pH 4.0) and cannot therefore be given parenterally. It is, however, effective by mouth and for this reason may eventually replace streptomycin, and even penicillin, in a wide range of infections. It has been used successfully in gonorrhœa, pneumococcal pneumonia, and penicillin-resistant staphylococcal infections. Several reports have appeared of its curative action in virus pneumonia (Schoenbach, 1949; Meiklejohn, 1949). Spink and his colleagues (1948) have recently described the successful treatment of human infection with *Brucella melitensis* by oral administration of aureomycin. The results were so striking that there is good reason to hope that aureomycin will provide the long sought remedy for human brucellosis. The only serious toxic effect was an initial febrile (?Herxheimer) reaction, which was avoided when small initial doses of the drug were used.

Chloromycetin (chloramphenicol) is derived from yet another member of the genus *Streptomyces*. It is effective when given by mouth and has recently been synthesized. Reports indicate that both the natural and synthetic products are effective against scrub-typhus (Smadel *et al.*, 1948, 1949). In

It is not inappropriate that in Jenner's centenary year *B.C.G. vaccination* should have been approved for clinical trials in this country. Large-scale experience on the Continent has produced convincing evidence of its effectiveness, and immunity lasting for five to ten years may be obtained. Schemes for widespread vaccination are being organized in India, where early trials have given encouraging results.

CONCLUSION

From this brief survey it is apparent that the past year has provided advances in medical treatment which stand fair comparison with any similar period in our history. Discovery, trial and assessment, and the process of rationalization are all richly represented. In attempting to summarize this story of the year's progress one is repeatedly reminded that treatment is still an affair of the individual patient, and is becoming no less so as therapeutic agents become more varied and more specific. Reflecting on this issue, it is apparent that an improved organization is required to make the appropriate treatment more promptly and certainly available for the individual patient. Few of us can any longer be expected to decide unaided the "intentions to be answered" by all the new remedies, for the machinery at present available is inadequate to bridge the gap between the medical scientist, the manufacturer and the practitioner. There is good hope that in the near future the deficiency may be made good, and that the efforts of teachers and investigators may be supplemented by administrative aid to remedy this "principal defect on the part of physic".

References

- Bethel, F. H., *et al.* (1948): *J. Lab. clin. Med.*, 33, 1477.
 Bradley, W. H. (1949): *Lancet*, i, 869.
 Bull, J. P., *et al.* (1949): *Ibid.*, i, 134.
 Cairns, H., and Taylor, M. (1949): *Proc. Roy. Soc. Med.*, 42, 155.
 Callender, S. T. E., *et al.* (1949): *Lancet*, ii, 57.
 Cathie, I. A. B. (1949): *Ibid.*, i, 441.
 Fowler, E. P. (1948): *Trans. Amer. Acad. Ophthalm. Otol.*, p. 293.
 Gay, L. N., and Carliner, P. C. (1949): *Bull. Johns Hopk. Hosp.*, 84, 470.
 Hench, P. S. (1949): *Proc. Mayo Clin.*, 24, 167.
 —, Kendal, P. C., *et al.* (1949): *Ibid.*, 24, 181.
 —, —, —, (1949): *Ann. rheum. Dis.*, 8, 97.
 Medical Research Council (1948): *Brit. med. J.*, ii, 769.
 Meiklejohn, G., and Shragg, R. I. (1949): *J. Amer. med. Ass.*, 140, 391.
 Ministry of Health Memorandum (1949): *Lancet*, i, 496.
 Moore, J. Earle (1949): *Ibid.*, i, 1009.
 Muirhead, E. F., *et al.* (1948): *Blood*, special issue, No. 2, 101.
 Schoenbach, E. B., and Bryer, M. S. (1949): *J. Amer. med. Ass.*, 139, 275.
 Smadel, J. E., *et al.* (1948): *Science*, 108, 160.
 — (1949): *Proc. Soc. exp. Biol. N.Y.*, 70, 191.
 Spink, W. W., *et al.* (1948): *J. Amer. med. Ass.*, 138, 1145.
 Thomas, E. W., *et al.* (1948): *Ibid.*, 137, 1517.
 Waksman, S. A., and Lechevalier, H. A. (1949): *Science*, 109, 305.
 Wilson, C. (1948): *Lancet*, ii, 485.
 Wilson, W. M., *et al.* (1949): *Ibid.*, i, 866.
 Woodward, T. E., *et al.* (1948): *Ann. intern. Med.*, 29, 131.

by a study of the essential metabolic requirements of bacteria. Fundamental research yields dividends in unexpected places, whilst empirical therapy may be strangely justified by events.

OTHER THERAPEUTIC ADVANCES

The foregoing represent the major therapeutic advances of the past year. In other fields there have been notable contributions—signs that the spirit of inquiry which in the past was directed to questions of diagnosis is now turning to the much more difficult problems of treatment. The application of *radioactive substances* is being pursued, but cautiously, as there are no means of assessing the genetic hazards involved. Useful work has been reported on the diagnosis and assessment of thyroid dysfunction by measuring the excretion of administered radioactive iodine, a technique which will greatly facilitate the proper use of anti-thyroid drugs.

Swedish workers have introduced a *new plasma substitute* in the form of a colloidal polysaccharide, "dextran", a by-product of the sugar refining industry. Trials in this country reported by Bull *et al.* (1949) confirmed the Swedish reports of its value in combating oligæmic shock, its slow removal from the blood, and its freedom from toxic reactions. There is evidence, however, that "dextran" remains for a long period in the tissues, and the possibility of harmful after-effects has delayed its more general application.

A chance discovery of considerable interest and practical value is the prophylactic and curative action of *antihistamine drugs in seasickness*. Gay and Carliner (1949) report the successful use of "dramamine", a new member of this group, in large-scale trials on American troops crossing the Atlantic. By contrast, Fowler (1948) has made use of the toxic effects of streptomycin on the labyrinth in the treatment of *labyrinthine disease*. Preliminary trials in *Ménière's disease* have shown that loss of vestibular nerve function may give relief from symptoms without producing nerve deafness. Further experience of this form of treatment is necessary, but the results reported offer a hope of relief in intractable cases when the disease is bilateral.

Advances in the treatment of *renal disease* are so infrequent that a rational and apparently successful approach to the problem of anuria is particularly worthy of note. During recent years there has developed an increasing interest in the suppression of urine which may follow trauma, incompatible blood transfusion, obstetric accidents and severe infections. Muirhead (1948) has emphasized the importance of maintaining salt and water balance during the development of the lesion through the phases of shock, anuria and polyuria. In the past there has been a tendency to give parenteral saline infusions in an effort to "force" renal excretion; too often this has accelerated the fatal outcome by producing pulmonary œdema. The new method of fluid and electrolyte control may well explain some of the successful results of dialysis techniques and is likely to replace the various devices aimed at supplying an "artificial kidney".

postural drainage positions, a masseuse sometimes assisting at the same time by thumping the chest. Should the blocked bronchus be a major one, the plug may need to be removed by suction through a bronchoscope; and in a ward where thoracic cases are regularly nursed, this instrument is no longer the monopoly of the oto-rhino-laryngologist. By these measures, together with preoperative radiological studies of the lungs in doubtful cases, progressive pulmonary complications have become a rarity.

Thrombosis and pulmonary embolism.—It has long been realized that the common source of emboli is the veins of the legs and of the pelvis. Many forms of treatment have been tried, but recent effort has been directed towards prevention. Some workers differentiate between thrombophlebitis and phlebothrombosis, the former inferring an inflammatory genesis, in consequence of which the clot is likely to be firmly adherent; the latter being a slow clotting, the result of stagnation from inactivity. It is well known that some patients will lie unnaturally still on a bed of sickness, assuming that any movement carries grave dangers with it. It is this silent phlebothrombosis that is dangerous, and early diagnosis is essential. Homans (1939) has written on this subject, and points out early minimal signs which make the diagnosis clear: slight fullness of the veins and blueness of the skin of the foot; slight masking of the extensor tendons of the toes by minimal œdema; tenderness of the calf muscles when pressed, and pain in the calf on dorsiflexion of the foot. Nowadays, it is customary to encourage frequent movement of the limbs in bed and early ambulation. In the larger hospitals the staff of the massage department conducts in-bed exercises and simple games, both before and after operation. No longer are abdominal cases kept flat on their backs for six to ten days; more often are they allowed up on the third or fourth day. Anything that encourages stagnation is eliminated, and this, when applied to the Fowler's position, may sound iconoclastic, but the "donkey" used in this position presses into the backs of the thighs and obstructs venous return. Since the introduction into my wards of these precautionary measures, thrombosis and embolism have become rare events.

One school of thought maintains that once the slightest suspicion of thrombosis is manifest, the main vein proximal to the clot should be ligated ("interrupted", as the Americans call it), even though this may mean the common iliac or even the vena cava. This policy has never been enthusiastically adopted in this country, and most surgeons here would give heparin in such cases, resorting to ligation only if one serious pulmonary embolism had occurred.

GASTRIC AND DUODENAL ULCER

In the past fifteen years the ratio between duodenal and gastric ulcers has altered to 8 to 1. The technique of partial gastrectomy has become so standardized that, when undertaken in conjunction with all the precautions and advances now available, its mortality is around 2 per cent., and physicians have sufficient confidence in surgical treatment to advise opera-

ADVANCES IN SURGERY

By F. A. R. STAMMERS, C.B.E., CH.M., F.R.C.S.

Professor of Surgery, University of Birmingham.

FIFTEEN years ago Moynihan expressed the view that surgery had reached its highest attainments; and at about the same time Gordon Taylor published his book "The Dramatic in Surgery", describing exceptional major surgical procedures that to-day appear on the routine operating lists of any teaching hospital. In fact, there have been enormous strides forward in the last fifteen years, since ideas and research evolving during the few years preceding 1939 were greatly accelerated by the quickening experience of war. Readily available blood; a better understanding of how to maintain the proper balance of body fluids, crystalloids and proteins; greatly improved anaesthesia; the sulphonamides and antibiotics; the development of the thoracic cavity as a broad highway of surgery, common to thoracic and general surgeons alike; these have combined to render major interventions astonishingly safe. Indeed, the present position is that, so far as the immediate postoperative state is concerned, almost nothing is impossible: the real question is: "Is this or that procedure compatible with physiological well-being and a life worth living"?

Twenty-five years ago neurosurgery, thoracic surgery and plastic surgery under a few pioneers were beginning to appear as sharply defined specialties in this country. They are now represented in every teaching hospital and, under the new National Health Act, every Region will have adequate services in these specialties. But, for further progress, it is important that part of the work of these three groups should be done under a common roof with general surgeons, so that a healthy exchange of ideas and pooling of experiences can take place, and the proper place for this is the teaching hospital of each region.

PREOPERATIVE PREPARATION AND POSTOPERATIVE CARE

In the past, much surgical effort was brought to nought by chest complications; and even worse was the tragedy of pulmonary embolism secondary to phlebothrombosis. Much attention has been turned to these two problems.

The chest.—Since the introduction of breathing exercises before and after operation, together with sulphonamides and penicillin for those with chronic bronchitis, the incidence of pneumonia has been greatly reduced. Collapse of part, or the whole, of the lower lobes of the lungs is especially common after upper abdominal or thoraco-abdominal procedures. This is due to plugs of mucus blocking bronchi and, if allowed to remain, the collapsed areas soon become infected. Smaller plugs can be shifted by breathing exercises and the encouragement of regular coughing in the

"functional". A few of these are cases of hiatus hernia, the symptoms of which are regurgitation of small quantities of food, especially on bending forwards, retrosternal discomfort, a feeling of epigastric fullness or pain, some degree of dysphagia and, sometimes, hæmatemesis. The regurgitation on forward bending is the characteristic feature, and I know of one patient who had extra long handles fitted to her brooms so that she had no need to stoop while doing her housework. When these symptoms present themselves a barium meal should be taken with the patient in the Trendelenberg position, when a herniation of the fundus beside the œsophagus will be revealed. The condition may be due to a congenitally short œsophagus, or it may result from recurrent œsophagitis which, in turn, leads to shortening of the gullet and upward traction of the cardia. The congenital type is often associated with absence of the left crus of the diaphragm. The treatment is surgical, the approach being through the left chest, the knuckle of fundus being freed and pushed below the diaphragm, whilst the latter is reconstructed by a plastic operation. The procedure is straightforward and the mortality is low, in spite of many patients being in the sixties.

CARDIOSPASM

Treatment of this condition has been very unsatisfactory, most palliative measures being uncomfortable, and most operations being followed, before long, by relapse. Heller, in 1914, introduced an operation similar in principle to that of Rammstedt for hypertrophic pyloric stenosis of infancy, although muscular hypertrophy in cardiospasm does not compare with the latter condition. With present-day interest in approaching upper abdominal lesions *via* the thoracic route, this operation has recently been adopted in this country. The longitudinal and circular muscle fibres of the lower œsophagus are cut vertically by a $1\frac{1}{2}$ inch incision, passing on to the stomach, down to and exposing the outer surface of the mucous membrane. The edges of the incision are separated with forceps, which allows the mucous membrane to bulge outwards, thereby widening the lumen. The operation may be performed either through an upper abdominal transverse or oblique incision, or through the left chest. Unless the victim of cardiospasm takes to the alternative treatment of mercury bougies with the relish of a sword swallower, he should be offered the Heller operation, since its mortality is low and its early results promise better than any other treatment.

CARCINOMA OF THE ŒSOPHAGUS

Until quite recently little but palliative measures was available for this dread condition, and gastrostomy, Symond's and Souttar's tubes, radium needles and radon seeds, and radiotherapy gave to the victim poor hope and little comfort. To Grey Turner we owe much for pointing the way to œsophageal surgery, and with modern advances it is natural that a direct attack should be tried on cancer of the œsophagus. The mortality is high, perhaps 50 per cent., but the alternative is a particularly wretched few

tion much earlier. Yet, in spite of partial gastrectomy being one of the most satisfactory operations of surgery, another surgical procedure has crept in, namely *vagotomy*. This is based on the work of Dragstedt (1945), who argues that duodenal ulcer is a psychosomatic disorder resulting from hypersecretion—especially nocturnal—hyperacidity and hypermotility, and that each of these is mediated through the vagi; and that complete section of these nerves will diminish this overaction. The operation is being tried with various degrees of enthusiasm at a number of centres in this country, but its efficacy is still *sub judice*, since it has only been used for about three years. It is recommended for duodenal ulcer and for stomal ulcer following gastro-enterostomy, and it can be performed through the abdominal or through the thoracic routes. The latter is undoubtedly the easier, but when there is any suggestion of pyloric stenosis, the former should be employed in order that the pylorus may be inspected, and, if thought necessary, gastro-enterostomy or pyloroplasty may be performed, since it must be realized that vagotomy weakens gastric peristalsis, and a potential stenosis may then become actual. Unfortunately, the anatomy of the vagi is very variable, and it is easy to miss some fibres, after which a recurrence of hypersecretion and high acidity may develop. A test for complete section is the insulin test meal (Hollander, 1944), details of which are to be found elsewhere.

The attractions of the operation are that it is shorter and of less severity than is partial gastrectomy, that the convalescence is easier, as light diet may be given earlier, that the immediate psychological improvement is most striking and, finally, that patients gain weight as no patient after partial gastrectomy ever does, e.g. $1\frac{1}{2}$ to 2 stones (9.5 to 10.7 kg.). There are, however, potential complications, the most serious being postoperative distension, the result of parasympathetic paralysis, and although this usually responds to acetylcholine drugs, such as mechothane, it is sometimes necessary to re-open and to perform a gastro-jejunostomy. Less serious than this are minor discomforts, such as foul eructations, postprandial fullness, and a tendency to diarrhoea, but they all pass off within six months. The disturbing thing about this simpler procedure, however, is that it is not absolutely free from a mortality rate, in addition to which a few patients develop dyspepsia again owing to reactivation of the ulcer.

My own opinion of the operation, based on an experience in my department of roughly 100 cases, is that it is useful for two types of patient, namely, the young man with a short history and no radiographic or symptomatic evidence of stenosis, and the elderly person, suffering much pain but constitutionally unfit for partial gastrectomy.

HIATUS HERNIA

This condition is being recognized more frequently. All practitioners from time to time meet the case of dyspepsia which defies diagnosis, all the usual investigations proving negative, with the result that the patient is labelled

During the past two-and-a-half years in my own department in Birmingham, we have carried out 7 total gastrectomies with 2 deaths, and 12 subtotal gastrectomies (Birmingham definition) with 1 death (Stammers, 1949). In spite of all this, however, the one single factor that will really make the position more hopeful, is earlier diagnosis; and this is difficult.

ULCERATIVE COLITIS AND ITS TREATMENT BY ILEOSTOMY AND THE RUTZEN BAG

This psychosomatic disorder is one of the most distressing to treat. All sorts of diets, drugs, vaccines, sera, and lavage have been tried, usually in vain. One of the most hopeful measures is ileostomy, yet many physicians hesitate to advise it since it is a heavy price for a comparatively young person to pay. Once done, however, it is remarkable what improvement takes place: frequent stools cease, pain disappears, weight is gained and energy returns, the only trouble being the attention required by the ileostomy, the expense of copious daily dressings, and the restriction in activities. Indeed, many patients, forgetting the former ill-health and pain of their colitis, beg for the ileostomy to be closed. The introduction of the Rutzen bag has altered all this (Hardy *et al.*, 1949). It is made of thin rubber and has a flat rubber flange which fits snugly over the ileostomy, and is then cemented by non-irritant rubber solution to the surrounding skin. The lower, dependent part of the bag, is controlled by a rubber band so that it may be emptied periodically during the day. A second bag is used at night, so that the first may be washed and dried ready for next day. With the aid of this device, and with the expenditure of about half-an-hour a day, patients may fulfil all their usual activities.

PORTAL HYPERTENSION

There is a group of conditions often referred to as Banti's syndrome, resulting from a block in some part of the portal venous bed and characterized by secondary anæmia, leucopenia, thrombocytopenia, splenomegaly and marked opening up of the collateral circulation, especially around the lower œsophagus and cardia, from which severe hæmorrhage may occur, but also on the anterior abdominal wall and in the anal canal. There may also be cirrhosis of the liver. The site of the venous block may be intra- or extra-hepatic, the former being associated with one of the forms of cirrhosis of the liver, a fact that may be proved by liver function tests. The extra-hepatic type of block may be due to fibrous stricture or cavernomatous transformation of the portal vein, or thrombosis or stricture of the splenic vein; and whichever of these it be, it leads to portal hypertension.

By long observation and brilliantly conceived experiments producing portal hypertension in animals, Whipple and his co-workers (1945) have gone far towards clarifying the Banti syndrome, and they argue that by switching the portal blood into the systemic circulation they would relieve the hypertension and thereby the hæmatemesis and ascites. Blakemore and Lord (1945), working with Whipple, perfected a technique whereby in man

months leading up to certain death, and there is little doubt that results will improve as experience is gained. The incision is usually along the 7th or 8th rib, continued obliquely forwards into the abdomen. After opening the diaphragm, the œsophagus with its growth is isolated, if need be as high as the arch of the aorta, and after excision the upper end is anastomosed to the stomach, which after mobilization has been drawn up into the chest. Success has attended this procedure and patients have been enabled to live comfortable lives; but this is not to deny that certain physiological difficulties may arise, especially with regard to œsophagitis, the result of frequent regurgitation of acid juices. The patient must sleep propped up on high pillows, and throughout the twenty-four hours must take alkalis frequently. These measures may prevent œsophagitis, but not always, and then the act of swallowing may become so excessively painful that the patient would prefer to starve.

CARCINOMA OF THE STOMACH

Statistics for cancer of the stomach are universally depressing and remarkably constant. Roughly speaking, half of all who report have already obvious metastases. If the other half are submitted to laparotomy, 50 per cent. are found to have such widespread dissemination as to preclude even a palliative operation, whilst half of the remainder admit only of palliative gastro-entrostomy. Only the residue, i.e., about 12 per cent. of the original number, offer any chance of a radical excision. Hitherto, only 1 per cent. of all cases of carcinoma of the stomach have survived for five years or more. It is hoped that modern methods may improve this appalling figure, and during the war years such leaders as Wangenstein (1943), Lahey (1944), Phemister (1943), and Allison and Borrie (1949) have not hesitated to remove the whole stomach and omenta, together with the spleen and have left half of the pancreas, if thought necessary. The operation can be performed through either the abdomen, the left chest, or through a combined route, and the jejunum is anastomosed to the œsophagus, using either a loop of the former with an entero-enterostomy or a Roux en-Y anastomosis. The object of these devices is to prevent pancreatic juices from coming in contact with œsophageal mucous membrane. For growths confined to the pyloric half, a subtotal (near-total) gastrectomy may be sufficient, provided that by this term is meant that the section passes through œsophageal mucous membrane on the lesser curve side and leaves no more than 4 cm. of fundus on the greater curve side. This operation can be done without opening the chest and there is less tendency to regurgitation than in the absence of this small rim of cardia. Subsequently, patients can eat meals of reasonable bulk and variety, and with reasonable speed. They tend not to gain weight and may suffer some mild diarrhœa, but they can undertake light work.

Time must pass before we know whether life has been prolonged for these patients, but these extended operations are undoubtedly worth continuing.

During the past two-and-a-half years in my own department in Birmingham, we have carried out 7 total gastrectomies with 2 deaths, and 12 subtotal gastrectomies (Birmingham definition) with 1 death (Stammers, 1949). In spite of all this, however, the one single factor that will really make the position more hopeful, is earlier diagnosis; and this is difficult.

ULCERATIVE COLITIS AND ITS TREATMENT BY ILEOSTOMY AND THE RUTZEN BAG

This psychosomatic disorder is one of the most distressing to treat. All sorts of diets, drugs, vaccines, sera, and lavage have been tried, usually in vain. One of the most hopeful measures is ileostomy, yet many physicians hesitate to advise it since it is a heavy price for a comparatively young person to pay. Once done, however, it is remarkable what improvement takes place: frequent stools cease, pain disappears, weight is gained and energy returns, the only trouble being the attention required by the ileostomy, the expense of copious daily dressings, and the restriction in activities. Indeed, many patients, forgetting the former ill-health and pain of their colitis, beg for the ileostomy to be closed. The introduction of the Rutzen bag has altered all this (Hardy *et al.*, 1949). It is made of thin rubber and has a flat rubber flange which fits snugly over the ileostomy, and is then cemented by non-irritant rubber solution to the surrounding skin. The lower, dependent part of the bag, is controlled by a rubber band so that it may be emptied periodically during the day. A second bag is used at night, so that the first may be washed and dried ready for next day. With the aid of this device, and with the expenditure of about half-an-hour a day, patients may fulfil all their usual activities.

PORTAL HYPERTENSION

There is a group of conditions often referred to as Banti's syndrome, resulting from a block in some part of the portal venous bed and characterized by secondary anæmia, leucopenia, thrombocytopenia, splenomegaly and marked opening up of the collateral circulation, especially around the lower œsophagus and cardia, from which severe hæmorrhage may occur, but also on the anterior abdominal wall and in the anal canal. There may also be cirrhosis of the liver. The site of the venous block may be intra- or extra-hepatic, the former being associated with one of the forms of cirrhosis of the liver, a fact that may be proved by liver function tests. The extra-hepatic type of block may be due to fibrous stricture or cavernomatous transformation of the portal vein, or thrombosis or stricture of the splenic vein; and whichever of these it be, it leads to portal hypertension.

By long observation and brilliantly conceived experiments producing portal hypertension in animals, Whipple and his co-workers (1945) have gone far towards clarifying the Banti syndrome, and they argue that by switching the portal blood into the systemic circulation they would relieve the hypertension and thereby the hæmatemesis and ascites. Blakemore and Lord (1945), working with Whipple, perfected a technique whereby in man

the splenic vein can be anastomosed to the left renal or the portal vein to the vena cava. This operation is being taken up in most centres in this country, and two series have recently been published by Learmonth (1949) and Milnes-Walker (1949). The operation is still on trial, since it has a mortality of about 40 per cent. At times the surgeon is prevented from carrying out the operation by a network of large and friable veins in the mesenteries and extra-peritoneal fat; and sometimes he is forced to acknowledge that the natural collateral bed is much wider than any artificial one that could ever be manufactured.

ESSENTIAL HYPERTENSION

The interest of the last twenty years in the surgery of the sympathetic nervous system as applied to peripheral vascular disease was bound to lead to its application in some form or other to the problem of essential hypertension. The pioneers were Adson, Peat, White and Smithwick. A more or less standardized operation has evolved, and White and Smithwick (1941) laid down rules regarding choice of case. The operation consists of bilateral excision of the splanchnic nerves down to the celiac ganglia, together with the sympathetic chain supplying them, that is to say, D₅ to L₁ or L₂. Cases regarded as suitable should not show any renal insufficiency, heart failure, or cerebral incidents, and only minimal retinal changes.

The value of the operation must remain *sub judice* until longer follow-up has been possible, but it is certain that the crippling headaches are cured, and in a number the blood pressure is apparently lowered. In many others, however, the blood pressure returns to preoperative levels within a few months, even though the headaches remain relieved. In assessing blood pressure it is necessary to take it in the sitting and standing postures, as well as with the patient lying down, since there is marked postural instability, so that whereas in the latter position the pressure may soon return to preoperative levels, with the patient standing it may well fall 30 to 40 mm. Hg. This is important, since it means that during much of the day the heart no longer has to work against the preoperative resistance.

In this disease the surgeon often finds himself persuaded against his will by the physician and coerced into operation by the declaration that unless something is done the patient will die within a short time. Partly because of this, in almost all centres more advanced cases are being submitted to operation—with papillœdema and hæmorrhages; having had one or more cerebral incidents; with albuminuria; and, more recently, with heart failure. One of the astonishing things about these cases is the low operative mortality—about 5 per cent.; and although there may be some alarming postoperative complications, such as drowsiness, faintness and even unconsciousness with the least elevation of the patient, these visceral and vascular features do clear up or improve.

Just as there is a change in view with respect to choice of case, there is also a tendency in many centres to remove more of the sympathetic chain,

e.g. D3 to L3, with the idea of reducing peripheral resistance in the limbs.

None would advocate operation for the symptomless hyperpietic discovered accidentally during life insurance examination, nor for one whose symptoms are easily controlled by medical means, but by operation much relief can be given for severe headache, dizziness, palpitation, breathlessness and visual disturbance, and many patients have been enabled to return to relatively active lives.

CONGENITAL HEART DISEASE

Some of the most dramatic of recent advances have been in connexion with congenital heart disease, particularly patent ductus arteriosus, the malformation known as Fallot's tetralogy, and coarctation of the aorta. To be sorted out properly these cases must be admitted under a team of workers familiar with cardio-pulmonary physiology and well experienced in the technique of cardiac catheterization, since there are many types of congenital heart lesions and these can only be differentiated by this method.

The names of Blalock and Taussig (1945) will always be associated with the original researches leading to the development of a successful operation for the "blue baby" of the Fallot type. It consists of anastomosing a systemic artery—usually the cut and down-turned left subclavian—to the pulmonary artery. In skilled hands it bears a mortality of about 16 per cent., and since the alternative is cardiac invalidism and certain death, most parents would wish to take this risk. The optimum age for operation is seven to ten years. Restoration to normal health can hardly be expected, but many are transformed from almost completely bedridden, cyanosed, breathless invalids to happy children, able to go to school and to take part in general activities.

Patent ductus arteriosus is easily dealt with: the operation consists of gentle blunt dissection of the patent vessel connecting the pulmonary artery and aorta, with ligation of each end. The mortality is low and the results are most successful.

References

- Allison, P. R., and Borrie, J. (1949): *Brit. J. Surg.*, 37, 1.
 Blakemore, A. H., and Lord, J. W. (1945): *Ann. Surg.*, 122, 4.
 Blalock, A., and Taussig, H. B. (1945): *J. Amer. med. Ass.*, 128, 189.
 Dragstedt, L. R. (1945): *Ann. Surg.*, 122, 973.
 Hardy, L. T., Brooke, B. N., and Hawkins, C. F. (1949): *Lancet*, ii, 5.
 Heller, E. (1914): *Mittheil. Grenzgeb. Med. Chir.*, 27, 141.
 Hollander, F. (1944): *Gastro-enterol.*, 3, 463.
 Homans, J. (1939): *New Engl. J. Med.*, 211, 993.
 Lahey, F. H., and Marshall, S. F. (1944): *Ann. Surg.*, 119, 300.
 Learmonth, J. R. (1949): *Proc. Roy. Soc. Med.*, 42, 6.
 Milnes-Walker, R. (1949): *Ibid.*, 42, 6.
 Phemister, D. B. (1943): *Arch. Surg.*, 46, 915.
 Stammers, F. A. R. (1949): *Proc. Roy. Soc. Med.* (in the press).
 Wangensteen, W. O. (1943): *Arch. Surg.*, 46, 879.
 Whipple, Allen O., et al. (1945): *Ann. Surg.*, 122, 4.
 White, J. C., and Smithwick, R. H. (1941): "The Autonomic Nervous System", New York.

the splenic vein can be anastomosed to the left renal or the portal vein to the vena cava. This operation is being taken up in most centres in this country, and two series have recently been published by Learmonth (1949) and Milnes-Walker (1949). The operation is still on trial, since it has a mortality of about 40 per cent. At times the surgeon is prevented from carrying out the operation by a network of large and friable veins in the mesenteries and extra-peritoneal fat; and sometimes he is forced to acknowledge that the natural collateral bed is much wider than any artificial one that could ever be manufactured.

ESSENTIAL HYPERTENSION

The interest of the last twenty years in the surgery of the sympathetic nervous system as applied to peripheral vascular disease was bound to lead to its application in some form or other to the problem of essential hypertension. The pioneers were Adson, Peat, White and Smithwick. A more or less standardized operation has evolved, and White and Smithwick (1941) laid down rules regarding choice of case. The operation consists of bilateral excision of the splanchnic nerves down to the celiac ganglia, together with the sympathetic chain supplying them, that is to say, D5 to L1 or L2. Cases regarded as suitable should not show any renal insufficiency, heart failure, or cerebral incidents, and only minimal retinal changes.

The value of the operation must remain *sub judice* until longer follow-up has been possible, but it is certain that the crippling headaches are cured, and in a number the blood pressure is apparently lowered. In many others, however, the blood pressure returns to preoperative levels within a few months, even though the headaches remain relieved. In assessing blood pressure it is necessary to take it in the sitting and standing postures, as well as with the patient lying down, since there is marked postural instability, so that whereas in the latter position the pressure may soon return to preoperative levels, with the patient standing it may well fall 30 to 40 mm. Hg. This is important, since it means that during much of the day the heart no longer has to work against the preoperative resistance.

In this disease the surgeon often finds himself persuaded against his will by the physician and coerced into operation by the declaration that unless something is done the patient will die within a short time. Partly because of this, in almost all centres more advanced cases are being submitted to operation—with papilloedema and hæmorrhages; having had one or more cerebral incidents; with albuminuria; and, more recently, with heart failure. One of the astonishing things about these cases is the low operative mortality—about 5 per cent.; and although there may be some alarming postoperative complications, such as drowsiness, faintness and even unconsciousness with the least elevation of the patient, these visceral and vascular features do clear up or improve.

Just as there is a change in view with respect to choice of case, there is also a tendency in many centres to remove more of the sympathetic chain,

morbidity and mortality. Sutherland (1946) has made a special study of the stillbirth rate and its relation to social influences, and has examined the probable factors responsible for: (a) geographical differences; (b) the maintenance of high rates and their gradual reduction in recent years; (c) the more abrupt decline in stillbirths which has taken place in the war years. He has adduced evidence that the common factor is improved nutrition. Denmark has always had lower stillbirth rates than England and at the same time has always been a well-fed country without wide social class distinctions. If the population of England and Wales could reach the same plane of nutrition as that in Denmark the number of stillbirths might be reduced by 6000 per annum. The reduction by 34 per cent. in the stillbirth rate in Wales during the war is a fact that should not pass unnoticed.

Before the war certain industrial areas were "black spots" so far as midwifery was concerned. With the better distribution of food, extra milk and vitamin supplements, and more efficient obstetric supervision, childbirth has become safer in these parts of the country. Emblin (1949) has shown how such an improvement can be achieved by the better integration of hospital, antenatal, domiciliary and specialist services. In the Halifax Municipal Obstetric Organization, he has recorded 5000 consecutive deliveries without a maternal death due to pregnancy.

CONDUCT OF PREGNANCY

Normal.—In 1947 there were 2,067 antenatal clinics provided by the local authorities and voluntary associations. Over 700,000 women received antenatal care either at these clinics or from private doctors in agreement with the local authorities. The magnitude of the service can be appreciated from these figures, and it behoves all those working in it to be alive to their responsibilities.

There has been an awakening to the fact that the better prepared a woman is for her labour the more likely is it to be normal. This applies especially to the amount of analgesia that she may require. The majority of women facing their first confinement are anxious about what lies before them. Yet how many of them are given a chance in busy antenatal clinics, to unburden their minds?

Several maternity centres have introduced a course of preparation for childbirth. This consists of lectures and demonstrations. At University College Hospital a programme has been evolved in which the physiology of pregnancy and labour is explained simply by a midwife with the use of diagrams, models, and so forth. A physiotherapist describes the pain-fear-tension syndrome of Dr. Dick Read and also the way in which it can be overcome. She teaches muscle relaxation and certain exercises, which are also practised at home. Questions are freely invited. Colleagues from the pædiatric department advise on the preparation for breast feeding and answer questions relating to the baby. The anæsthetist demonstrates different forms of analgesic apparatus which the mothers handle.

ADVANCES IN MIDWIFERY

By W. C. W. NIXON, M.D., F.R.C.S., F.R.C.O.G.

Professor of Obstetrics and Gynaecology, University of London.

THE reduction of maternal mortality by more than three-quarters in fifteen years is a remarkable achievement. All the more noteworthy are the low records of maternal and infant mortality that have been reached, despite the interval of the war years (table 1).

Is this improvement due to better obstetric practice? There are those who claim that this is the sole reason. Yet there are factors apart from advances in

TABLE 1
MORTALITY RATES IN ENGLAND AND WALES (1939-48)

Year	Live Birth Rate per 1000 Total Population	Maternal Mortality Rate including Abortion per 1000 Births	Still-birth Rate per 1000 Total Births	Neo-natal Mortality Rate* per 1000 Related Live Births	Infant Mortality Rate per 1000 Related Live Births
1939	14.8	3.13	38	28.28	51
1940	14.1	2.68	37	29.61	57
1941	13.9	2.80	35	29.00	60
1942	15.6	2.48	33	27.23	51
1943	16.2	2.29	30	25.22	49
1944	17.7	1.93	28	24.35	45
1945	15.9	1.80	28	24.76	46
1946	19.2	1.43	27	24.46	43
1947	20.5	1.17	24	22.70	41
1948	17.9	1.01	23	19.70	34

* i.e. Deaths under 4 weeks.

technique and the management of the complications of pregnancy and labour that have contributed. For instance, many more mothers come under antenatal supervision at an earlier date in pregnancy. There is a wider and more serious attempt to keep pregnancy normal rather than await complications and all the sadistic drama that surrounds them. More and more emphasis is being laid on prevention, and with the increasing practice of family limitation the preservation of infant life is all the more imperative. The nonchalant attitude towards the wastage of infant life that existed in the Victorian era is no longer found to-day; the survival of the newborn is a concern not only of the family but of the nation.

Social factors are assuming increasing importance, and there is abundant proof that women in the lower social classes are exposed to greater hazards when having their babies than their better-off sisters. If this group were able to have the same attention during pregnancy, parturition and the puerperium that mothers in social class I (Registrar-General's classification) receive, then there would be an immediate drop in maternal and infant

limit of normal blood pressure in pregnancy has been recognized as 140/90, mm. Hg, but there is an increasing tendency to lower this figure and adopt 120/80 mm. Hg as the standard.

The interest in hypertension has shifted to those cases in which a rise of blood pressure is found early in pregnancy—so-called “chronic or essential hypertension”. At the recent British Congress of Obstetrics and Gynaecology, Browne (1949) reviewed this subject to which he has given so many years of study. He is of the opinion that chronic hypertension contributes about 25 per cent. of all forms of toxæmia of late pregnancy, and when it is accompanied by diminished kidney function, severe arteriosclerosis or albuminuric retinitis, continuation of the pregnancy is dangerous to the mother. The blood pressure rises in about 60 per cent. of other cases during pregnancy, and in about one-third of these albuminuria develops and intra-uterine death usually occurs. When the blood pressure at the start of pregnancy is 150/100 mm. Hg or over, the outlook for the fœtus is poor. The immediate risk to the mother is either eclampsia or a cerebral catastrophe. It seems that the hypertension is not permanently aggravated by the pregnancy unless the patient develops superimposed pre-eclamptic toxæmia or eclampsia.

Treatment.—In the uncomplicated case it is usual to allow pregnancy to continue, but if early in pregnancy the blood pressure is more than 150/100 mm. Hg the prognosis for the fœtus is bad and termination is indicated. Again, when the blood pressure rises over 160/100 mm. Hg and albumin appears in the urine the outlook for the fœtus is serious. The aim of treatment should therefore be to keep the tension below this critical level, and at present this can be done only by rest. It is usual to prescribe one of the barbiturates. Unfortunately there is no drug which will maintain a permanent reduction of blood pressure. Tetraethylammonium bromide, pentamethonium iodide (C₅), or potassium thiocyanate are disappointing.

One of the difficulties of treatment is to know when to terminate the pregnancy. During the last few weeks of pregnancy, toxæmia with its high fœtal mortality may be an added complication, and this at a time when the fœtus is premature. One may interfere too early before the fœtus is mature enough to survive, or too late, with resultant death *in utero*. Every effort is made to coax the pregnancy to the 36th week, when it should be terminated. There is an increasing tendency to deliver these cases by Cæsarean section under local or spinal anæsthesia. In this way the fœtus is subjected to the least possible trauma. But even by this method of delivery certain survival of the baby cannot be guaranteed.

PREGNANCY IN THE DIABETIC

Pregnancy in the diabetic has always been associated with a high fœtal mortality. With the introduction of insulin and proper control the risk of pregnancy to the mother has become almost negligible, but there has not been a corresponding fall in the number of stillbirths and neonatal deaths.

ANTEPARTUM HÆMORRHAGE

The two most common causes of bleeding after the 28th week of pregnancy are *placenta prævia* and *accidental hæmorrhage*. It is the treatment of the former that has altered. There was a time when bleeding from placenta prævia was considered a major emergency and pregnancy was immediately terminated, no matter the amount of the hæmorrhage or the period of gestation. An early attempt at diagnosis was made by digital examination of the lower uterine segment. This often provoked further bleeding, and with this the fœtus died and the mother became exsanguinated and later sometimes succumbed to infection. Maternal mortality was about 6 per cent. and fœtal mortality over 50 per cent.

By conservative treatment these figures have been much reduced. Macafee (1949) has published a series of 275 cases from the Royal Maternity Hospital, Belfast, in which the maternal mortality was 0.73 per cent. (no death from hæmorrhage or shock) and the gross fœtal mortality was 20.4 per cent. The most important cause of fœtal mortality is prematurity and any treatment that will help to increase maturity will therefore save infant life. There is another factor which is at present difficult to eliminate, and that is fœtal abnormalities. The association of this complication with placenta prævia varies from between 3 to 4 per cent.

The case which is to be treated expectantly has to be selected with care. There is no justification for embarking on this treatment when hæmorrhage occurs after 38 weeks' gestation. In Macafee's opinion "the case in which expectant treatment is most valuable is the one where a small hæmorrhage has occurred at 30 to 34 weeks, where the baby is premature, and where the baby's chance of survival is much improved if the pregnancy can be prolonged three to four weeks. An additional and important factor is the amount and duration of the hæmorrhage". Expectant treatment should only be undertaken in a hospital, where a full blood examination should be done. The vagina should not be examined but a speculum should be passed to see whether the bleeding is due to an obvious vaginal or cervical cause.

Active treatment is usual after the 38th week or when there has been a severe hæmorrhage and abdominal examination points to placenta prævia. It should be carried out in the operating theatre, for upon the degree of placenta prævia so Cæsarean section will be indicated. In the third or fourth degree—marginal or central of the old nomenclature—Cæsarean section is the usual treatment. For the lesser degrees, artificial rupture of the membranes often suffices.

HYPERTENSION IN PREGNANCY

The importance of observing the blood pressure in pregnancy is receiving more and more emphasis. A rise of blood pressure has long been recognized as one of the early signs of pre-eclamptic toxæmia. If more attention were paid to this and treatment instituted earlier the incidence of these cases of grave toxæmia with their heavy fœtal loss would be reduced. The upper

and in recent months have modified the dose. When contractions are becoming painful the initial dose has been increased to 150 mg. Several hours later a second injection may be needed, and then the amount given is 100 mg. If pethidine is given too early it does cause delay in labour. In spite of the favourable results, study of this drug is still being continued in order to achieve the optimum effect, that is, the greatest relief for the mother without delaying labour or depressing the respiration of the baby.

An old and established friend, *chloral hydrate* (30 grains [2 g.]), remains a useful drug in the early stages of labour. There is a combination widely known as "mother's mist." A single dose of bromide apparently is not pharmacologically effective, and the third ingredient, tincture of opium, in one hospital mixture, for example, amounts to only $7\frac{1}{2}$ minims (0.5 ml.), the equivalent of $1/16$ grain (4 mg.) of morphine. The continued use of this mixture seems hardly justified.

In our view *barbiturates* are not indicated in labour but they may be given before labour has begun in order to relieve anxiety. When these drugs are pushed to the extent of producing stupor the life of the baby is jeopardized.

Omnopon ($\frac{1}{2}$ a grain [20 mg.]) and *scopolamine* ($1/150$ grain [0.43 mg.]) is a combination favoured by many practitioners. There are two types of case in which this is indicated: (1) when a mother is seen rather early in labour and at night, and is unduly apprehensive; and (2) when trial labour has continued for some time and the drugs mentioned previously have proved inadequate. In this type additional sedation may be needed, and rectal ether ($2\frac{1}{2}$ ounces [75 ml.]) in olive oil ($1\frac{1}{2}$ ounces [45 ml.]), or rectal paraldehyde (240 minims [14 ml.]) in olive oil (2 ounces [57 ml.]) can be recommended. Again, chloral hydrate (30 grains [2 g.]) may be used with the injection of omnopon and scopolamine. Repeated injections of scopolamine are not advisable as with this drug some mothers become disorientated and unmanageable. Of *heroin* I have not had any experience. A recent report has shown that it increased the incidence of asphyxia neonatorum. It is known to be more depressant upon the respiratory centre than morphine.

It is important to reiterate that a parturient woman should not be allowed to go without sleep for twenty-four hours.

As already stated, more and more attention is being paid to the condition of the baby at birth. The worst possible result of an analgesic drug is that it paralyses the respiratory centre and the baby dies from asphyxia. There are degrees of asphyxia, and what is exercising the attention of pædiatricians is the possibility of permanent damage to the cortical cells in non-fatal asphyxia. Investigators have noted that children who have suffered anoxia at birth have developed convulsions, or again, impaired intelligence, as compared with their siblings. So there is this additional and remote danger which must be taken into account when advising upon obstetric analgesia.

There is a tendency to rely over-much upon the hypodermic needle or the tablet as part of a stereotyped system to relieve the pain of uterine contrac-

Workers in the United States have published figures of much lower foetal loss as the result of hormone therapy. Credit must be given to Smith and Smith (1934), who revealed the hormone imbalance that is found in abnormal pregnancy. They were interested in the problem of pregnancy toxæmia and chose a series of diabetic pregnancies since there is such a high incidence of pregnancy toxæmia in diabetics. They found an increased amount of chorionic gonadotrophin in the serum of those women who developed toxæmia. Later, they showed a low œstrogen level in the urine and serum of diabetic women with superadded toxæmia. There was also a low pregnanediol excretion in this group. A theory has been advanced that the source of progesterone and œstrin in pregnancy is the syncytial cells in the placenta. In toxæmia there is syncytial degeneration, so that the placenta cannot utilize chorionic gonadotrophin for the formation of progesterone and œstrin. The Smiths (1948) have shown that *stilbæstrol therapy* helps to maintain the balance between chorionic gonadotrophin, œstrin and progesterone. White (1947) has achieved remarkable results with hormone therapy and has improved the foetal survival rate to 90 per cent., reducing the incidence of toxæmia to 5 per cent. Treatment should be started early in pregnancy with stilbæstrol 5 mg. three times a day, increasing to 135 mg. by the 34th week.

The *time and method of delivery* has been a subject of much controversy. Oakley and Peel (1949) have had an extensive experience of pregnancy in diabetes at Kings College Hospital, London, where the incidence of diabetic pregnancy is about 1:50 pregnancies. They are of the opinion that 36 weeks is the optimum date for termination in the absence of special indications for earlier or later interference. They have found that the combined foetal loss from fresh stillbirth and neonatal death is greatest in spontaneous and induced labour. The baby of a diabetic mother tolerates labour very badly, especially if it is prolonged, and uterine inertia is more common. They are firm in their view that Cæsarean section under local or spinal anæsthesia carries with it the lowest foetal mortality if undertaken at the 36th week. In 213 Cæsarean sections they had only one maternal death.

OBSTETRIC ANALGESIA AND ANÆSTHESIA

A subject which has received much attention is *obstetric analgesia*, but the ideal type of analgesia in childbirth has not yet been attained. Space does not allow of a recital or appraisal of the many drugs and their combinations that have been used to relieve the pain of labour. It has been realized that babies have died from asphyxia resultant upon the transplacental influence of the drug. It is poor consolation for a mother to have a painless delivery only to be told when she wakes from her torpor that her baby is dead. Sometimes the effect of the analgesic is not lethal, yet it may cause many anxious minutes to the attendants during their efforts to revive an asphyxiated baby.

At University College Hospital we have established the value of *pethidine*,

placenta had been left *in utero* for three to seven hours. He has also shown how shock increases with the duration of retention of the placenta. No matter how brutal the delivery, if the uterus is empty within an hour of delivery, obstetric shock is an unusual complication.

There are now hospitals where an intravenous injection of an oxytocic drug (pitocin, 5 units, or ergometrine, 0.125 mg.) is given routinely with the birth of the head. There are others where this practice is restricted to operative delivery in which an anæsthetic is given. The impression gained is that by this technique the third stage of labour becomes an almost bloodless procedure, but the incidence of manual removal of the placenta is raised.

POSTPARTUM REHABILITATION

The present tendency is to start early movement, not only after operations but also after deliveries. It has long been appreciated that venous stasis predisposes to thrombosis. With a view to measuring the rate of venous blood flow in the legs of women at term and in the puerperium, Wright *et al.* (1949) at University College Hospital have been using radioactive sodium. Foot-groin venous blood flow estimations showed a great retardation of the venous flow in the legs of patients during labour; in the puerperium, however, the rate of venous flow returned rapidly to normal and was almost identical with that of non-pregnant subjects.

With early ambulation the patient is out of bed by the third day. Within twenty-four hours of delivery the mother sits on the edge of the bed and swings her legs. A physiotherapist also instructs her in breathing and exercises. After forty-eight hours the mother stands and walks round the bed. On the fourth day she should be able to walk to the toilet. Soldenhoff (1948) has given a year's trial to early rising and is convinced that it is better than keeping the mothers in bed for ten to fourteen days. Respiratory complications are reduced and there is less need for catheterization. The length of stay in bed for thrombophlebitis cases was reduced by fourteen days. In those centres where early ambulation is practised there is general support for it from patients, nurses and medical personnel.

References

- Browne, F. J. (1949): *Trans. Brit. Congr. Obstet. Gynec.* (in the press).
 Dieckmann, W. J., *et al.* (1947): *Amer. J. Obstet. Gynec.*, 54, 415.
 Emblin, N. (1949): *Brit. med. J.*, i, 260.
 Macafee, C. H. G. (1949): *Post-grad. med. J.*, 25, 297.
 Oakley, W., and Peel, J. (1949): *Trans. Brit. Congr. Obstet. Gynec.* (in the press).
 Sheehan, H. C. (1949): *Brit. med. J.*, i, 849.
 Smith, G., and Smith, O. W. (1934): *Amer. J. Physiol.*, 107, 128.
 ———, ——— (1948): *Amer. J. Obstet. Gynec.*, 56, 821.
 Soldenhoff, R. de (1948): *Lancet*, ii, 961.
 Sutherland, I. (1946): *Ibid.*, ii, 953.
 White, P. (1947): *Pennsylv. med. J.*, 50, 705.
 Wright, H. P., *et al.* (1949): *J. Obstet. Gynec. Brit. Emp.*, 56, 35.

tions. Too often is it forgotten that there is an individual with her own particular personality who should play an active part in her own delivery. It is an indubitable fact that the better the mother is prepared for her confinement during pregnancy the less analgesic drug she will need. It should be obligatory for all those who work in antenatal clinics to devote some of their time to allaying the fears that beset the expectant mother. Analgesic apparatus should be demonstrated in the antenatal clinic, and every expectant mother shown how to use it.

An obstetric department is failing in its service to the community if its personnel does not include an anaesthetist who has made, or is making, a special study of the particular problems that arise in obstetric analgesia and anaesthesia. The aim should be to ensure that a woman receives all the help that science can give in such a way that she can experience that fulfilment and joy which are her natural right.

POSTPARTUM HÆMORRHAGE

Hæmorrhage now occupies second place as a cause of maternal mortality. Antepartum hæmorrhage has already been mentioned, and the way in which it can be controlled. But deaths from postpartum hæmorrhage are four times as common as from antepartum hæmorrhage, and the complications of the third stage of labour equal those of the first and second stages together. Even in well-regulated institutions the incidence of postpartum hæmorrhage is between 2 and 3 per cent. Most cases of postpartum hæmorrhage are due to atony, and bleeding from the placental site is controlled: (1) by the contraction of the uterus which compresses the vessels; (2) by retraction—permanent shortening of the muscle bundles—which constricts the vessels; and (3) by thrombosis at the placental site.

At the Chicago Lying-in Hospital, Dieckmann (1947) has developed a technique by which one unit of pituitary is injected intravenously with the birth of the posterior shoulder. The incidence of postpartum hæmorrhage has been reduced from 1.36 per cent. to 0.35 per cent. He is of the opinion that the placenta begins to separate as the baby is born and that it can be expressed normally within one to three minutes after delivery. For the proper separation of the placenta slow delivery of the baby is of the utmost importance. Dieckmann pauses thirty seconds after the delivery of the anterior shoulder and sixty seconds after the posterior. In this way the uterine wall is given time to contract and retract and tears itself away from the placenta.

The old practice of waiting hours for the delivery of the placenta, even in the absence of hæmorrhage, is fast disappearing. Manual removal of the placenta is now practised within an hour of delivery. Sheehan (1949) has examined 98 patients at autopsy who died from retained placenta and postpartum hæmorrhage. Most of the deaths occurred in cases in which the

infection, either clinically, serologically or radiologically. In the two abortions, syphilis did not appear to be causative. In three-quarters of the cases treatment was not started until after the fourth month of pregnancy.

Immunization.—The problem of immunizing infants against whooping-cough and diphtheria at a much earlier age than the customary six to nine months has been the subject of considerable work. *Whooping-cough* is fatal in a high percentage of cases in the first six months of life, and as few infants carry over any appreciable immunity from their mothers the possibility of early immunization—starting even in the neonatal period—is certainly worthy of investigation. Some few years ago Cohen and Scadron immunized mothers in the third trimester of their pregnancies and found that the infants derived a quite appreciable immunity in the early months by this method. It was long thought that the very young infant had but poor powers of antibody formation; this is now disproved. Although antibody production undoubtedly increases throughout the first year of life, adequate response may follow immunization at as early an age as six weeks. It is thus possible and practicable to immunize infants against pertussis at this age. In the case of *diphtheria*, however, passively transmitted maternal immunity, which occurs in about 50 per cent. of infants, may interfere with the development of active immunity following A.P.T., and immunization is better delayed until three months of age.

With the mass immunizations that have taken place in recent years, there is an alteration in the immunity of the population as a whole, and subclinical infections, acquired from carriers, which acted as stimulators of immunity, are now much less prevalent. As a result, repeated doses of A.P.T. and pertussis vaccine are necessary at intervals throughout childhood if satisfactory titres are to be maintained in the blood. They may be given, combined, at two- or three-yearly intervals. Pertussis vaccine, in dosage of 20,000 million organisms, should also be given after any known exposure to whooping-cough.

The problem of *diphtheria carriers*, for long an insoluble one, has shown signs of solution since the introduction of penicillin, and encouraging results have been published following aerosol therapy (Legros, 1947), and after systemic treatment (Wernstein, 1947). Legros reported a 90 per cent. clearance after four days' treatment with 100,000 units of penicillin dissolved in 4 ml. normal saline and inhaled for ten minutes daily. Wernstein recommended 250,000 units daily by intramuscular injection for twelve days.

The prevention of *tuberculosis* is still an outstanding problem. B.C.G. vaccination has for a number of years been employed in infancy in various parts of the world, particularly in Scandinavia, and has proved both successful and safe. It may be that this will be the next great advance in preventive pædiatrics in this country.

CARE OF THE NEWBORN

There is renewed interest in the nursing of new-born infants in maternity

ADVANCES IN PÆDIATRICS

By WILFRID GAISFORD, M.D., F.R.C.P.

Professor of Child Health, University of Manchester.

CURATIVE and preventive pædiatrics have both shown steady progress during recent years and there is evidence of much closer cooperation between hospital pædiatricians and infant welfare and school medical officers, to the mutual benefit of both and, even more important, of the children. The general practitioner also, who is responsible for the care of most of the childhood population throughout the country, is being considered in this progress by the increased time in the medical curriculum which is being allotted to the subject of child health and pædiatrics. Instruction is now being given for three months in most medical schools (including one month's residence), with a view to ensuring that all students on qualifying have a more adequate basic knowledge of the problems of health and disease in infancy and childhood. Although the two aspects, health and disease, are closely linked together, it is convenient in reviewing recent progress to consider them separately.

PREVENTIVE MEASURES

As regards child health, or the prevention of disease in childhood, there have been a number of striking advances. The publication of the Ministry of Health report on Neonatal Mortality and Morbidity (1949) has been perhaps the most noteworthy and helpful addition to the literature on this subject. It should be read by all who have the care of new-born infants, as well as by obstetricians and maternity medical officers.

The preparation of a rhesus hapten by Carter (1947), if her work can be confirmed and the hapten produced in adequate quantity, is an important contribution to the treatment of *haemolytic disease of the newborn*, and may result in its being included among the preventable diseases. By the use of this substance, a lipoid fraction obtained from group O rhesus-positive blood, Carter succeeded in lowering the antibody titre in a number of sensitized mothers. She has reported (1949) a series of 30, either treated or undergoing treatment, and also recorded the results with 27 affected babies, twenty of whom recovered, fourteen without any transfusion and the other six with a single transfusion each of less than 100 ml.

Another disease which could, and should, be prevented is *congenital syphilis*. The results of treating the mother antenatally with penicillin, even if treatment is not begun until after the fourth month of pregnancy, are excellent. Tucker (1949) treated 149 syphilitic pregnant women, and 127 had normal full-term infants, 16 were delivered prematurely but the infants survived, and 2 aborted. In no case was there any evidence of syphilitic

rheumatism was twenty times greater in the control group. Kuttner also reported further series treated with sulphathiazole, sulphamerazine and sulphadiazine with comparable results. The dosage was small, varying from 0.25 to 0.5 g. daily. Despite the undoubted value of such a form of therapy, the development of resistant strains of streptococci is a serious drawback. Stokes (1947) found that a significant rise in sulphonamide-resistant organisms occurred in the throats of children given 0.5 to 1.5 g. daily as a prophylactic. Rosenberg and Hench (1946), however, made no mention of this in collecting data of over 1000 children treated with prophylactic sulphonamide between 1939-45. Recurrences of rheumatism were found in 2.2 per cent. as compared with 13.7 per cent. in the controls, and they concluded that such prophylaxis was therefore well worth while.

Maliner (1947) obtained good results with *penicillin* orally, tablets of 5000 units being sucked after meals. Lapin (1948) treated a large series for a year with 50,000 units twice daily, in the form of buffered tablets given before breakfast and supper, and found that upper respiratory infection and recurrences of rheumatism were much less than in a control group.

Sheldon (1948) has made the valuable suggestion that the school medical officer should, in conjunction with the general practitioner, play a much larger part in the detection of early rheumatism, which is essentially a disease of school age, by following up all children who have been absent from school with a sore throat. From three weeks to one month after their attack of throat infection these children should be seen and examined with special reference to the possibility of early cardiac involvement. Sheldon also supports the idea originally put forward by Schlesinger (1938) that this period is the ideal time to prevent the development of rheumatism by giving a course of *sodium salicylate*.

Although it has recently been suggested that rheumatism is becoming less frequent in children, it is still a major problem. The importance of maintaining an adequate plasma salicylate level is now recognized. Most children will tolerate the 1.5 grains per pound (0.1 g. per kg.) body weight per day necessary to produce such a level. The value of giving *vitamin K* concurrently, because of the hypoprothrombinæmia resulting from salicylate administration, has been stressed, and Shapiro (1944) has shown that 1 mg. of vitamin K for each 1 g. of sodium salicylate will neutralize any hæmorrhagic tendency.

CURATIVE PÆDIATRICS

Chemotherapy.—More figures are available of the long-term results of the treatment with *streptomycin* of children suffering from *tuberculous meningitis* and *miliary tuberculosis*. It is clear that the ideal drug has not yet been found. The term "cure" can be applied only to a small percentage of cases of meningitis, although the figures for miliary tuberculosis are much more encouraging. The introduction of dihydrostreptomycin (Hobson *et al.*,

hospitals in cots at their mothers' bedside rather than in nurseries. The advantages are many and the results excellent. This really psychological procedure might well be adopted—or rather re-adopted, for it was the normal order of things many years ago—in plans for new maternity units: small groups, 2, 4 or 6, preferably not more, mothers with their infants being nursed together. This regime certainly helps the relationship between mother and infant and is particularly valuable educationally to primiparae. It encourages breast feeding and the adoption of a mutually satisfactory feeding time-schedule between mother and infant. It is also of value in stressing to students and resident medical officers the "child health" aspect of neonatal life and progress as opposed to the neonatal pathology, which usually attracts greater attention. The abolition of the large (though often not large enough) nurseries limits the risks of infection and of epidemics. It is the opinion of some psychiatrists that the behaviour problems encountered in older children attending child guidance clinics would be fewer if this method were more widely adopted.

Rickets and *scurvy* are both being seen more often than in recent years and there is need to re-emphasize the importance of impressing on mothers the reasons for their having to give their infants cod-liver oil and orange juice, or their equivalents, in adequate doses *regularly*. There is still a widespread belief among mothers that orange juice is given primarily for the baby's bowels and that if they are opened normally the juice need not be continued. Similarly, if cod-liver oil is not accepted readily by the infant a mother will often discontinue giving it, but will not tell her doctor that she has done so. Direct questioning of the mother at each visit to the welfare clinic or doctor is the only way of ascertaining with certainty that every infant is getting a daily addition of vitamins, and so of preventing these diseases.

RHEUMATIC INFECTIONS

The problem of preventing, or minimizing, recurrences of rheumatic infection has been tackled along two main lines: first, diet and environment, and secondly, prolonged treatment with sulphonamides or penicillin to prevent the upper respiratory infections which precede the rheumatic exacerbations. Jackson *et al.* (1947) found that recurrences were diminished when special attention was paid to the diet, particularly when more protein and less carbohydrate were given. Environment was found to be an important factor only in that social group corresponding to our Registrar-General's Class V. They concluded that an excellent diet and a high level of environmental care would practically eliminate the chances of recurrence with carditis. Where such diet and care were not available they considered that chemotherapeutic prophylaxis was indicated.

Sulphonamides.—Kuttner (1947) treated a series of rheumatic children with sulphanilamide for two consecutive winters and observed a comparable control series. The incidence of streptococcal pharyngitis and of recurrent

Procaine penicillin G in 2 per cent. aluminium monostearate will produce an adequate blood level for twenty-four hours, so that injections, even in cases of severe infection, need only be given once daily. For meningococcal and pneumococcal meningitis, 500,000 to 2,000,000 units may be given. In favourable cases, only two or three such injections may be necessary. In *H. influenzae* infections a combination of sulphadiazine and streptomycin seems to produce the best results. Because of the rapidity with which this organism becomes resistant to streptomycin a large initial dose is imperative. Streptomycin, 0.5 to 1 g. according to age, may be given six-hourly, and sulphadiazine, 1 to 4 g., followed by 0.5 to 1 g. six-hourly. Penicillin may be of value if streptomycin resistance occurs before the infection is overcome, and treatment may have to be continued for some time. Alternatively, three or four separate intensive courses lasting for twenty-four hours may be given at three- to four-day intervals. This method has given excellent results in influenzal meningitis. The indication for repeating the course is the infant's general condition, *not* the state of his cerebrospinal fluid. It is seldom necessary to do more than one lumbar puncture.

Gastro-enteritis in infancy has been the subject of continued research, both from the point of view of fluid requirements and of bacteriology. Bacteriological investigations have naturally led to extensions of the chemotherapeutic approach. The etiology of epidemics of diarrhoea in early infancy, and particularly in the neonatal period, is still obscure. Various viruses have been implicated in some outbreaks, staphylococci in others, a non-motile type of *B. coli* (*B. neapolitanum*) in others, and no pathogenic organism at all in yet others, so that it is improbable that any one single etiological agent is responsible. The most fertile field for investigation has been the *B. neapolitanum*, which has been found in a number of different areas in the country, but its pathogenicity is still uncertain. Because of the rapidity with which this organism becomes resistant, a short but intensive course of streptomycin is necessary. The usual dose is 20 mg. per pound (22 mg. per kg.) body weight per day, given four-hourly. If no improvement occurs within five days, a change of antibiotic is indicated. In many cases the results have been most satisfactory, but it is quite possible that the good effects have been due to the control of the secondary infections which are so often present in these cases, particularly of the upper respiratory tract and middle ear.

Some progress has been made with *cœliac disease* and cystic fibrosis of the pancreas. The work of Andersen (1947) and Sheldon (1949) has stressed the importance of omitting starch rather than fat from the diet in cœliac disease; the results of high-protein, low-fat and starch-free diets are truly remarkable. The principles of treatment are that milk must be modified, protein provided in approximately twice the normal quantity, and starch and dextrin excluded from the diet. Soya bean flour is a suitable alternative for making bread and biscuits. Fat intake should be low but need

1948) may diminish the incidence of toxic complications, particularly in the nervous system, and so allow of a higher dosage. More potent and less toxic antibiotics active against *B. tuberculosis* are even now undergoing clinical trial.

For the *extrathoracic tuberculous infections* and for minimal lesions needing treatment, oral administration with *p*-aminosalicylic acid (P.A.S.) has proved valuable. In doses of 1 to 5 g. daily, which are adequate, toxic reactions have been few, although rashes may necessitate a diminution or even temporary cessation of treatment.

Tuberculous cervical adenitis, especially the acute form, has responded well to chemotherapy. Systemic streptomycin and oral P.A.S. both produce good results and in cases in which softening has already occurred aspiration and replacement with 100,000 units of streptomycin dissolved in 1 ml. of sterile water may well obviate the need for surgical intervention. The aspiration may have to be repeated once or twice, with similar streptomycin instillation, at weekly intervals, before subsidence finally occurs. Tuberculous peritonitis likewise has shown prompt improvement after both streptomycin and P.A.S., symptoms clearing within a week or ten days of the beginning of treatment.

Other chemotherapeutic substances recently introduced are aerosporin, chloromycetin and aureomycin. These have proved effective in a wide range of infections. Aerosporin, given orally, has produced results in the treatment of gastro-enteritis in infants comparable with those following streptomycin. Chloromycetin has been found effective in typhoid fever, and aureomycin in *B. abortus* infection and *atypical pneumonia*. It is still too early to evaluate their true worth, but they are all compounds of promise and, of great importance in paediatrics, may be administered orally. Optimal dosage cannot yet be determined but the recommended courses are: (a) for aerosporin in gastro-enteritis, a course lasting up to five days if necessary, using 20 mg. per pound (22 mg. per kg.) body weight per day, in divided doses four-hourly; (b) for chloromycetin, an initial dose of 0.5 to 2 g., according to age, followed by 0.25 g. four-hourly; and (c) for aureomycin, 0.25 g. (250,000 units) four-hourly.

Meningitis due to organisms other than *M. tuberculosis* has been subjected to a variety of treatments from time to time, culminating in the routine intrathecal administration of one or other chemotherapeutic or antibiotic at frequent intervals, often daily. Recent work has shown that intrathecal treatment is not necessary (certainly not as a routine) to effect a cure. Hoyne and Brown (1948) obtained better results in *H. influenzae* meningitis without using intrathecal injections, and Dowling *et al.* (1949) reported similar findings in pneumococcal meningitis. This means that meningitis may come to be added to the list of infections in infancy and childhood which may, in suitable cases, be treated at home in the future. The use of the latest depot technique for penicillin administration brings this a stage nearer.

B.A.L. IN PINK DISEASE

The etiology of acrodynia (pink disease) remains unproven, but the suggestion made by Warkany and Hubbard (1948) that it is due, in some cases, to an idiosyncrasy to mercury has met with a certain amount of confirmation. In Manchester, for example, where the condition is common, there is a history in almost every case of the ingestion of mercury, usually as calomel in teething powders (which may contain 25 per cent. or more of calomel), and in the urines of affected infants an excess of mercury—that is, over 5 μ g. per 100 ml.—has been found in three-quarters of the cases, the average figure being 75 μ g. per 100 ml. (Varley, 1949). The treatment of severe cases, recommended when mercury is present in the urine, is with B.A.L., in doses of 1 mg. per pound (1.1 mg. per kg.) of body weight, given four-hourly for one day, and then twice daily for ten days, by which time improvement should have occurred. B.A.L. may be prescribed in a 10 per cent. solution in oil. Bivings (1949) reported cure or prompt improvement in eleven of fifteen children so treated. It must be remembered that B.A.L. is a toxic compound and reactions (anorexia, restlessness, vomiting, fever and convulsions, and the presence of a reducing substance in the urine) may occur if excessive or too long-continued dosage is given. According to Tye and Siegel (1947) such toxic symptoms may be prevented by giving ephedrine sulphate, $\frac{1}{4}$ of a grain (16 mg.), half an hour before the injection of B.A.L.

References

- Andersen, Dorothy H. (1947): *J. Pediat.*, 30, 564.
 — (1949): *Pediatrics*, 3, 406.
 Bivings, L. (1949): *J. Pediat.*, 34, 322.
 Carter, Bettina (1947): *Amer. J. clin. Path.*, 17, 646.
 — (1949): *J. Immunol.*, 61, 79.
 Dowling, H. F., et al. (1949): *Amer. J. med. Sci.*, 217, 149.
 Farber, S., et al. (1948): *New Engl. J. Med.*, 238, 787.
 Hobson, L. B., et al. (1948): *Amer. Rev. Tuberc.*, 58, 501.
 Hoyne, A. L., and Brown, R. R. (1948): *J. Amer. med. Ass.*, 136, 597.
 Hughes, J. G., Jordan, R. G., and Hill, F. S. (1949): *Pediatrics*, 3, 801.
 Jackson, R. L., et al. (1947): *J. Pediat.*, 31, 390.
 Kuttner, Ann G. (1947): "Advances in Pediatrics", London, p. 367.
 Lapin, J. H. (1948): *J. Pediat.*, 32, 119.
 Legros, J. (1947): *Acta pædiatr. Belg.*, 1, 80.
 Maliner, M. M., and Amsterdam, S. D. (1947): *J. Pediat.*, 31, 658.
 Ministry of Health (1949): "Neonatal Mortality and Morbidity", *Rep. Publ. Hlth. med. Sub.*, No. 94, H.M. Stationery Office.
 Rosenberg, E. F., and Hench, P. S. (1946): *Med. Clin. N. Amer.*, 30, 489.
 Schlesinger, B. (1938): *Lancet*, i, 593.
 Shapiro, S. (1944): *J. Amer. med. Ass.*, 125, 546.
 Sheldon, W. (1948): *Acta pædiatr., Stockh.*, 36, 383.
 — (1949): *Arch. Dis. Childh.*, 24, 81.
 Stokes, H. L. (1947): *Proc. Roy. Austrl. Coll. Phys.*, 2, 16.
 Tucker, H. A. (1949): *Amer. J. med. Sci.*, 217, 157.
 Tye, M., and Siegel, J. M. (1947): *J. Amer. med. Ass.*, 134, 1477.
 Varley, H. (1949): Personal Communication.
 Warkany, J., and Hubbard, D. M. (1948): *Lancet*, i, 829.
 Wernstein, L. (1947): *Amer. J. med. Sci.*, 213, 308.

not be so rigidly restricted as is customary. A high intake of vitamin A and vitamin D is desirable: 3000 units of A, and 1500 units of vitamin D daily. A recent advance of importance is the production of a water-soluble mixture of these vitamins: an aqueous dispersion in propylene glycol which can be given in the feeds or in fruit juice. It is particularly valuable for use in coeliac disease, but is also a noteworthy aid in the care of premature babies, in whom the need for vitamins is great and whose fat absorption is, at best, restricted.

In *cystic fibrosis of the pancreas*, which is by no means a rare disease, the problems of preventing and treating the recurring pulmonary infections are most important. Andersen (1949) believes that dietary regulation will help in preventing these complications and that life will be prolonged thereby. Aerosol therapy offers the best form of treatment when pulmonary infection has occurred, penicillin and streptomycin being the drugs of choice. *Staphylococcus aureus* is usually the predominant organism but is quickly replaced by *B. coli* after penicillin aerosol therapy. When this occurs, change to streptomycin is indicated.

Not only have there been advances in chemotherapy by the development of new compounds and by the synthesis of some of the antibiotics, for example, chloromycetin, but certain types of malignant disease have proved responsive, at least in part, to chemotherapeutic attack. *Leukæmia* has been inhibited (i.e. remissions have ensued following treatment) by the folic acid antagonists *methopterin* and *aminopterin* (Farber *et al.*, 1948). Again, it is too early yet to assess the final worth of these drugs but they have shown more promise than any other method of treatment yet employed in this hitherto uniformly fatal disease of childhood.

THE "HYPO-SPRAY"

The last two years have witnessed the development of a method by which drugs might be introduced subcutaneously in sufficient quantity to give the desired results without the use of needle or syringe. The method is practically painless, and has the added advantage that no sterilization is required, the drug being contained in a sealed ampoule of either 0.25 or 1 ml. capacity, which is discarded after use. The instrument used is called a "hypo-spray". By the release of a powerful spring in the hypo-spray the fluid in the ampoule is forced out through a minute orifice in its anterior end, which is firmly pressed against the skin, as a finely divided jet which enters the tissues at an estimated speed of 600 m.p.h. This new technique has been found of special value in immunizations and for penicillin and streptomycin administration. Adequate blood titres and levels are obtained (Hughes *et al.*, 1949). Local anæsthetics may be given by this method, and its value in such conditions as diabetes and tuberculous meningitis, which demand long-continued parenteral treatment, is obvious.

arising from precipitation of iron in the blood. Nevertheless, with refractory patients or when a speedy result is essential, the intravenous route must be employed, and modern preparations are greatly in advance of those available a few years ago. A preparation (B.P.C.), consisting of a solution of saccharated oxide of iron containing about 3 per cent. of metallic iron in sucrose, has been favourably reported upon by Nissim (1947) and Slack and Wilkinson (1949) and has, in my own experience (1949), been highly successful and well tolerated. A reliable form of the material is made by Benger's Limited, under the trade name of "ferrivenin". This is dispensed in 5 ml. ampoules containing 100 mg. iron as a 2 per cent. solution. Each 5 ml. should, theoretically, cause a 4 per cent. rise in hæmoglobin.

FOLIC ACID

Folic acid, which in animals appears to stimulate the production of red cells, leucocytes and platelets, has been tried in a number of anæmias and other disorders of the blood in human beings. In practice, however, folic acid has been found to be hæmopoietically active only in the same groups of anæmias in which liver therapy is successful. These are the anæmias associated with megaloblastic erythropoiesis, which include pernicious anæmia, nutritional megaloblastic anæmia, megaloblastic anæmia of pregnancy, megaloblastic anæmias which accompany the sprue syndrome, and certain rare megaloblastic anæmias of undetermined origin. Folic acid also brings about a remarkable improvement in the diarrhœa and clinical state in sprue. Folic acid is ineffective in anæmias associated with normoblastic erythropoiesis.

In practice, the usefulness of folic acid has become clearly defined and its limitations appreciated. In pernicious anæmia, for example, by reason of failure to protect against or cure neurological complications, folic acid finds no place in routine treatment, despite the convenience of oral administration. For limited periods, folic acid may justifiably be used, such as when travelling or during a period when desensitization to liver is being carried out. In sprue, folic acid finds a most valuable place, not so much on account of hæmopoietic action as because of its remarkably beneficial effect on the general condition; folic acid should supplement rather than replace other treatment. In the megaloblastic anæmias of pregnancy and of nutritional origin, folic acid can be regarded as being the equal of liver extracts, although not all the pregnancy anæmias may respond; ease of administration and avoidance of gastric upset are often advantageous. In refractory anæmias of megaloblastic type, folic acid may sometimes be found to be the only effective agent. Animal experiments, which suggested that folic acid would have an active leucopoietic and thrombocytopoietic action, have found little confirmation in the human field. In principle, some effect may be anticipated when neutropenia or thrombocytopenia are due to malnutrition, rather than to toxic or constitutional causes.

ADVANCES IN THE TREATMENT OF BLOOD DISEASES

By SIR LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P.

Regius Professor of Physic in the University of Cambridge.

THE hæmopoietic system has to ensure a continuous supply of all elements of the blood in order to make good the everyday wastage. This fundamental function may be disturbed by nutritional deficiencies, by depressants such as toxins, sepsis or malignant growths, or by an inability to keep pace with the demand when blood destruction or blood loss is excessive. In times of stress the hæmopoietic system has to exhibit a flexibility enabling it to rise rapidly to an occasion and to respond appropriately to a given stimulus. Hence, we find that the main problems in so-called "blood diseases", by which we mean diseases in which there is some alteration in the normal blood picture, are either to determine why the hæmopoietic system is not performing its normal function or to determine the factor which is giving rise to abnormal blood changes.

Most "blood diseases" are secondary phenomena and this basic fact should be prominent in the mind when attempting to interpret hæmatological changes. Recent advances in the field of "blood diseases" are to be found in the therapeutics of hæmopoietic deficiency states, in attempts to control the malignant leucæmic process, and in the fundamental pathology of the hæmolytic anæmias.

IRON DEFICIENCY ANÆMIAS

Iron deficiency can almost always be effectively treated by the administration of appropriate amounts of iron salts, preferably ferrous salts, by the mouth. In some patients, however, this treatment is associated with unpleasant symptoms and gastro-intestinal disturbance; in others, the duration of the course may be wearisome; in others also, the treatment may not be completely successful because of poor absorption. Iron may be given by intramuscular or intravenous injection, and in either case there is always efficient absorption and storage; but there are a number of technical difficulties usually associated with the parenteral administration of iron. In the case of intramuscular injection, if the amount of iron injected be raised to an effective level, the injection is usually painful and the result sometimes dangerous.

As to intravenous injection, it must be borne in mind that iron is not transported in the ionic state. It can therefore be assumed that an intravenous injection of iron, which contains even minimal amounts of ionic iron, is liable to be badly tolerated. Intravenous injection may also be complicated by thrombophlebitis, and sometimes by embolic phenomena

assessed on its merits, and carefully selected. A preliminary period of observation with conservative treatment in the way of blood transfusion is always advisable in those whose main presenting symptom is anæmia or even thrombocytopenia. Cases with a palpable spleen and an impotently hyperplastic marrow usually respond well to splenectomy.

HÆMOLYTIC ANÆMIAS

During recent years important advances have been made towards the understanding of the group of anæmias in which a hæmolytic process forms the basic pathology. Most work has been done in the anæmias arising from Rh incompatibility due to the action of hæmolysins, which are sometimes revealed by direct examination, and at other times by the indirect technique of Coombs. Coombs' test, when applied to other hæmolytic anæmias, has clearly differentiated the hæmolytic state caused by a congenital abnormality of the corpuscles, such as congenital hæmolytic icterus, and so-called "acquired" types of hæmolytic icterus in which the anæmia is due to a circulating hæmolysin. The differentiation is important, in that transfusion in the congenital types is usually well tolerated and the transfused blood survives for a normal period, whereas the "acquired" or "hæmolysinic" types need to be most carefully tested before transfusion is undertaken, in order to ensure that the transfused corpuscles do not themselves adsorb the hæmolysin and suffer rapid destruction. In that the spleen is believed to be the source of the hæmolysins, splenectomy is a rational procedure in the "acquired" types, and is usually resorted to unless spontaneous recovery occurs without treatment or as the result of carefully matched transfusion.

Erythroblastosis fœtalis is ordinarily treated by the simple transfusion of appropriate blood, but the most modern technique is to effect a complete exchange of blood. This is claimed to reduce the mortality of the disease to some 22 per cent. (van Loghem *et al*, 1949). Mollison and Cutbush (1948) have summarized the points in favour of exchange transfusion in circumstances when a single transfusion of Rh-negative blood is not likely to suffice. These include an urgent need to raise the hæmoglobin level without increasing the blood volume, the reduction to the minimum of the destruction of Rh-positive cells during the critical first four days of life, and the providing of the infant with such a concentration of Rh-negative cells at one operation so that no further transfusions are needed. Various routes are used, including the umbilical vein, when the transfusion is carried out within a few hours of birth. The exchange is usually made with a 20 ml. syringe which, by means of three-way stopcocks, permits alternate withdrawal of infants' blood and infusion of donor's blood (adjusted by removal of plasma to have a red cell content of 5 to 6 million per c.mm.) to an amount of 400 to 500 ml. This achieves an exchange of the order of 80 to 90 per cent. The blood must be warmed.

VITAMIN B₁₂

Neither the purest liver extract nor folie acid has proved to be the hæmopoietic principle, extrinsic factor or intrinsic factor, all of which have defied isolation for more than twenty years. Modern methods of partition chromatography, however, appear to have solved one of the problems, but it is by no means certain whether the pure material, provisionally known as vitamin B₁₂, can be designated on Castle's theory as the hæmopoietic principle or the extrinsic factor.

Vitamin B₁₂, the most remarkable advance in hæmatological therapeutics since Minot's discovery of the efficiency of liver, the isolation of which was reported almost simultaneously by Lester-Smith (1948) and Rickes *et al.* (1948), is a crystalline compound highly active in pernicious anæmia in microgramme quantities. It has been obtained from ox-liver as well as from commercial liver extracts. The material itself crystallizes in the form of small red needles which contain the metal cobalt—a fact of extreme interest in view of the importance of this trace element in the prevention of anæmia in ruminants and rodents. Preliminary trials suggest that vitamin B₁₂ has a potency some 10,000 times that of folie acid, and promise that a satisfactory clinical response will be obtained in pernicious anæmia with as little as 20 to 60 µg. per day, or even less. The material, which is not yet available for general clinical use, is of extreme interest in that, unlike folic acid, it is active, not only from the hæmopoietic aspect, but also in relation to the neurotrophic lesions in pernicious anæmia.

HYPERSPLENISM

There is no doubt that the spleen exerts a considerable influence upon blood formation and may be greatly concerned with certain clinical states in which the peripheral blood picture suggests an aplastic or hypoplastic state. The peripheral cytopenia may affect leucocytes, red cells or thrombocytes, singly or in combination, leading to leucopenia, an aplastic type of anæmia, a hæmolytic anæmia or a thrombocytopenia. This pathological action of the spleen is termed *hypersplenism*, and the overactivity appears to be either primary or idiopathic, or secondary and due to hypertrophy of the spleen, as in syphilis, Gaucher's disease, sarcoidosis, malaria, Hodgkin's disease, or with induced hæmolysins. In such cases, the bone marrow may appear hyperplastic—impotently so, nevertheless—or may show a maturation arrest of one or more of the different series of cells.

In hypersplenism the normal inhibiting mechanism of the spleen is exaggerated. Inhibition of the appropriate element causes a non-hæmolytic aplastic anæmia, neutropenia or thrombocytopenia, respectively. In addition, the enlarged spleen may be overactive in its destructive function and thus cause a hæmolytic type of anæmia. In such states, splenectomy is beneficial and sometimes dramatically curative. But each case needs to be

ment than the acute types, but it is as well to realize that even the most modern treatment does not appear to achieve anything more than a prolongation of efficiency, as distinct from a prolongation of life. The most prominent symptom in leukæmia, and which inevitably develops during the course of the disease, is anæmia. This is ordinarily intractable unless the leukæmic process remits or is controlled, in which case the anæmia improves spontaneously. Treatment designed to restrain or control the leukæmic process is based on the fact that mitosis in dividing cells is inhibited or prevented by physical factors, such as ionizing radiations and certain anti-mitotic drugs. Ionizing radiations may be derived from X-rays, radium or radioactive isotopes, such as radiophosphorus (P^{32}), which is selectively absorbed by bone, or radiosodium (Na^{24}), which is generally distributed. Anti-mitotic drugs include arsenic, benzol, colchicine, urethane, nitrogen-mustard derivatives and pterins (folic acid antagonists). These substances, by temporarily limiting the degree of leukæmic hyperplasia and leukæmic infiltration, often cause improvement in secondary features such as anæmia or pressure symptoms. Treatment needs to be controlled carefully by regular hæmatological examinations, in order that the inhibiting process may not proceed to the length of causing agranulocytosis, severe thrombocytopenia and aplastic anæmia.

Arsenic is an efficient anti-mitotic substance which was used for the treatment of leukæmia, and with success, long before the introduction of modern methods; its use tends, undeservedly, to be neglected owing to the urge to seek for new things. Some patients may be controlled and kept comfortable with arsenic alone, and it is certainly the best form of treatment for pregnant women. Arsenic is used as a rule in the intervals between treatment with X-rays or radium; it should never be used concurrently.

Irradiation is an effective form of treatment in the majority of chronic cases of leukæmia, but irradiation sickness is common, whilst in many the treatment produces profound depression. The technique of treatment with either X-rays or radium is highly specialized and extremely variable, according to the views of the individual radiotherapist.

The results of treatment with *radiophosphorus* (P^{32}), which has a half-life of 14.3 days, are comparable with those obtained with X-rays, but not substantially better. Freedom from irradiation sickness is a practical advantage which those who have endured X-ray therapy greatly appreciate. On the other hand, a serious and incalculable disadvantage is the great variation in individual susceptibility. Some tolerate large amounts of the order of 30 millicuries, whilst others may rapidly develop thrombocytopenia with hæmorrhagic symptoms, or severe anæmia with eventual aplasia and agranulocytosis, with less than 5 millicuries. The usual dose is 1 to 2 millicuries once or twice a week. In general, it seems unlikely that radiophosphorus will ever displace the more conventional X-ray treatment. *Radiosodium* (Na^{24}) has the short half-life of 14.8 hours; it is absorbed after

POLYCYTHÆMIA VERA

Polycythæmia, an apparently benign form of hyperplasia, may be treated with the radioactive isotope of phosphorus (P^{32}) which has a half-life of 14.3 days. When injected intravenously this isotope is almost entirely absorbed selectively by bone, and so subjects the marrow to irradiation in gradually decreasing strength over a period of some weeks. Polycythæmia vera is the one striking example of success with radiophosphorus in the clinical field. Satisfactory remissions lasting for two, and sometimes five, years have been reported. A single intravenous injection of 3 to 8 millicuries of P^{32} is made. If the red cell count remains persistently high, a second (and sometimes a third) injection of 1 to 5 millicuries is given from three to six months later. Red meat, liver and kidney must be omitted from the diet, otherwise a remission may almost immediately be inhibited.

ACUTE LEUKÆMIA

In the acute forms of the disease the most that can be expected is a temporary and usually fleeting remission. Temporary improvement has been claimed to follow the use of "aminopterin" (see p. 296) in acute leukæmia in children, but the claim is by no means substantiated. Transfusion of fresh blood has for long been the only form of effective ameliorative treatment, and it is instructive to note that as long ago as 1924, Sabin *et al.* reported that transfusions apparently induced maturation of myeloblasts in a patient with subacute myeloblastic leukæmia. More extensive modern studies with massive transfusions or exchange transfusions have shown that the treatment may not only bring about maturation of the primitive cells, but also may cause the whole blood picture to revert to normal and bring about a subsidence of splenic and glandular enlargement as well as a clinical remission of distressing symptoms such as hæmorrhage and anæmia. In these observations may lie a germ of hope for treatment in the future, for if normal blood contains a factor which will create order out of disorder, the isolation of that factor should open an approach to treatment more rational than modern methods which aim at inhibiting mitosis, rather than encouraging normal maturation.

Experience has shown that this phenomenon of remission in acute leukæmia in response to massive transfusion may be obtained with considerable regularity, using either fresh blood or fresh plasma, but not with reconstituted dried plasma. Dreyfus (1948), in reviewing the literature of remissions in acute leukæmia, came to the interesting conclusion that when remissions are recorded they have almost always followed transfusions of blood or plasma.

CHRONIC LEUKÆMIA

The chronic forms of leukæmia have always been more amenable to treat-

disease for periods of a few months; it is not permanently curative. Pentamidine has also been used with success when stilbamidine has failed, but the latter is preferable. A reasonable level of renal efficiency is desirable before undertaking the treatment.

A common sequel to treatment is a dissociated anæsthesia of the trigeminal nerve, which occurs some months later, but is of little clinical importance. No benefit is obtained unless the treatment is combined with a low protein diet. Irradiation treatment may with advantage follow the course of stilbamidine.

CONCLUSIONS

Advances in the study of blood diseases during the past few years have shown not only how numerous are the growing points in the subject of hæmatology, but also how growth may begin in the most surprising places. Who would have thought that the academic study of the metabolic requirements of an unimportant bacillus would have led to the impingement of folic acid upon hæmatology? This in itself has forged an important link in the understanding of hæmopoiesis, and has given rise to new ideas for the treatment of leukæmia. Who would have thought that the production of a lethal gas for the destructive purposes of war would have led to a useful remedy for Hodgkin's disease and opened up a field of investigation which may take years to explore? It may well be that the blood diseases will eventually prove to be the field in which new ground will be broken in relation to the cause and treatment of malignant processes.

References

- Dreyfus, B. (1948): *Rev. d' Hématol.*, 3, 29.
Lester-Smith, E. (1948): *Nature*, 162, 144.
Mollison, P. L., and Cutbush, M. (1948): *Lancet*, ii, 522.
Nissim, J. A. (1947): *Ibid.*, ii, 49.
Rickes, E. L., et al. (1948): *Science*, 107, 396.
Sabin, F. R., et al. (1924): *J. exp. Med.*, 40, 845.
Slack, H. G. B., and Wilkinson, J. F. (1949): *Lancet*, i, 11.
Snapper, J. (1946): *J. Mt. Sinai Hosp.*, 13, 119.
van Loghem, J. J., et al. (1949): *Brit. med. J.*, ii, 49.
Whitby, L. E. H. (1949): *J. Roy. Inst. pub. Hlth. Hyg.*, 12, 88.

oral administration and becomes widely distributed throughout the body. The effect appears to be intermediate between that obtained with radio-phosphorus and general irradiation.

Urethane has a similar effect to X-rays, with the advantage of ease of administration (by mouth) and the relative infrequency of unpleasant effects compared with X-rays. Intolerance is shown by nausea, vomiting or, less commonly, diarrhoea and drowsiness. Not all patients react favourably, and treatment has to be controlled carefully, otherwise serious thrombocytopenia may arise. The effects continue for some time after the withdrawal of the drug. The usual dose is $\frac{1}{2}$ to 1 g., three or four times a day, administered by mouth. *Urethane* elixir (Boots) contains 1 g. of urethane in 7.5 ml. and is a very suitable preparation.

Two modifications of mustard gas known as *bis-* and *tris-nitrogen mustard* have been used for the treatment of various neoplastic conditions, including Hodgkin's disease and leukaemia. Both have almost the same action, but the *bis* form is generally considered to be less toxic. Nitrogen mustard is not suitable for acute leukaemia and does not appear to be more effective than X-rays in chronic leukaemia, although improvement has been noted in cases resistant to irradiation. No cure has been obtained. The dosage is 0.1 mg. per kg. body weight, administered intravenously daily or every second day for one to seven days. Boots Pure Drug Co. supply the *bis* compound in 10 mg. vials, to which 10 ml. of saline is added as a diluent before intravenous injection. Toxic effects include pain, inflammation and even thrombosis at the site of injection, with necrosis of local tissue if leakage or extravasation occurs. Within an hour of injection there are usually systemic symptoms, such as anorexia, nausea, vomiting, headache and vertigo.

Pterine compounds include diapterin, teropterin and aminopterin. The last named has been most used, and temporary improvement has been observed in acute leukaemia. The results in chronic leukaemia have been uneven and mainly disappointing. It would not seem that these folic acid antagonists, in their present form, are likely to prove of value, but at least they open up a field of investigation and research. The pterins must be regarded as of fundamental importance, in that they are definitely related to a substance which the body uses normally, and therefore point the way to a line of treatment far more physiological than such destructive agents as X-rays.

MYELOMA

Snapper (1946) was the first to treat cases of myeloma with stilbamidine combined with a diet low in animal protein, on the grounds that the drug is effective in kala-azar which, like myeloma, is characterized by hyperglobulinaemia. Clinical reports show that stilbamidine treatment may cause a remarkable relief of pain in a high proportion of cases and may check the

satisfactorily to its use. Like other drugs of the same category, it can cause a sensitization dermatitis.

Streptomycin and calciferol.—Because the use of streptomycin carries the hazard of certain complications, particularly ataxia and deafness, its use in dermatology has yet to be decided. When these hazards are overcome—possibly by the introduction of a derivative of the antibiotic—we shall have an admirable weapon, even more potent than calciferol, to combat *tuberculous infections of the skin*. Already it is known that intramuscular injections of streptomycin in divided doses totalling 1 to 2 g. daily for a period of seven to nine weeks, will cause great recession and perhaps cure of *lupus vulgaris*. Cornbleet (1948) has suggested that calciferol and streptomycin act as synergists when given concurrently. This is debatable, but some cases of *lupus vulgaris* which have failed to respond to calciferol will respond to streptomycin. Those readers who have seen something of the modern treatment of *tuberculosis cutis*, and who remember the dolorous path which was trodden by patients with *lupus vulgaris* fifteen years ago, will appreciate that the introduction of calciferol treatment by Charpy in Dijon, and Dowling and Prosser Thomas in London, followed so soon by the introduction of streptomycin, marks the beginning of an era in therapeutics which will be noted by the medical historians in future years.

Phenylmercuric nitrate.—To pass now to an entirely different matter: the incidence of *tinea capitis* underwent one of its periodic increases in recent years, and this stimulated research both in the United Kingdom and in the United States of America. The mycologists seem to have reached the conclusion that most cases due to *Microspora*, other than *M. audouini*, and particularly those due to *M. felineum*, can be cured without epilation by the persevering application of the usual fungicidal and fungistatic remedies. Infections with *M. felineum* are fairly common in many parts of the country, and therefore some dermatologists now arrange for the culture and identification of the fungus from each case before deciding to remove the hair by X-rays or thallium acetate. Infections with *M. audouini* are more difficult to cure and for these epilation, followed by the application of a suitable fungicide, is still the best routine measure; but if the parents object to epilation, procedures such as those suggested by Brain *et al.* (1948) may be employed. Those interested in this matter should refer to the original paper by these authors; briefly, they recommend that phenylmercuric nitrate, 0.5 per cent., incorporated in a special base should be employed. The hair is cut short all over the scalp, and every morning the head is thoroughly washed. The ointment is applied thrice daily, and cure may be expected in many cases in two to three months. Sufficient data are not available to state what the rate of cure should be; at present it is not likely to be higher than 75 per cent.

Undecylenic acid.—Recently we have had opportunities in this country to test the view expressed by Shapiro and Rothman (1945) that preparations

ADVANCES IN THE TREATMENT OF SKIN DISEASES

By R. M. B. MACKENNA, M.D., F.R.C.P.

Physician in charge of the Dermatological Department, St. Bartholomew's Hospital; Physician, St. John's Hospital for Diseases of the Skin.

At present, advances in the treatment of skin diseases depend upon three principal factors which may be classified thus:—

- (1) The introduction of new drugs.
- (2) The application in therapy of measures discovered or suggested by studies of metabolism or of the endocrine system.
- (3) The increasing use of psychiatry in the treatment of cutaneous diseases.

These factors will be discussed seriatim.

THE INTRODUCTION OF NEW DRUGS

Penicillin.—Dermatology has profited by the introduction of antibiotics in much the same manner as many other branches of medicine, and as this matter has been fully discussed in *The Practitioner* on several occasions, only a few items in this field will be mentioned here. So far as penicillin is concerned, it will suffice to emphasize that we now know that in cases of *chronic furunculosis* which are not associated with systemic disease, injections of penicillin produce only temporary amelioration. The reason appears to be that multiple boils are but a symptom of a breakdown in the mechanism of self-disinfection of the skin, for one can readily culture from areas remote from the lesions pathogenic staphylococci which are not present in significant numbers on healthy skin. These invaders are not greatly affected by the injections of penicillin for they are present on the epidermis where the antibiotic cannot reach them in concentrations adequate to annihilate them. Soon after the course of injections is over they are available in large numbers to produce more boils and carbuncles. In the treatment of chronic furunculosis the most successful therapy depends upon methods well established in former years which need not be discussed here; possibly it is worth noting that a seaside holiday with plenty of sun- and sea-bathing is often more beneficial than the measures described in books.

Tyrothricin is now available in Great Britain. It has been used as a local application, particularly to combat pyogenic infections in and around the hair follicles, for many strains of *Staphylococcus aureus* and *Streptococcus pyogenes* are tyrothricin sensitive. The use of the antibiotic does not seem to have made any great progress in practice, although some lesions respond

MEASURES SUGGESTED BY STUDIES IN METABOLISM AND ENDOCRINOLOGY

Insulin.—Urbach and Lentz (1945) suggested that there is an independent, intermediary carbohydrate metabolism in the skin. They believed that in certain stubborn skin conditions, such as chronic furunculosis, sweat-gland abscesses, and certain eczemas and prurites, although the glucose tolerance test might give blood levels within the limits of the normal, skin sugar tests might show that the skin sugar levels were abnormally high; (a skin-sugar level above 68 mg. per 100 grammes of skin is said to be pathological).

It is not too much to say that this view was received with considerable scepticism in many quarters, and from the scientific aspect the whole of the data should be corroborated or disproved. But from the clinical aspect it is worth remembering that in many cases of the type referred to, improvement is considerably hastened if the patient is instructed to keep to a low carbohydrate diet; in some cases of pyoderma in which there is no evidence of diabetes, injections of 5 units of insulin immediately before breakfast and dinner (or supper) are followed after a short period by marked improvement. The efficacy of the treatment may be shown by noting a relapse of the eruption if the treatment is discontinued too soon. It is obvious that insulin can be used in this manner safely only if facilities exist for reasonably full examination of the case before insulin treatment is begun; and only if other measures have failed and the patient is kept under adequate supervision.

Recent experience has amply confirmed the view that in some intractable intertriginous and eczematous eruptions in middle-aged or elderly persons, although glycosuria is not noted, a glucose tolerance test shows that the patient has an abnormal carbohydrate metabolism, and the eruption will not improve until a full diabetic regimen is prescribed.

Œstrogens.—Both in America and here, there has been some important work concerning *acne vulgaris*, but certain basic problems remain unsolved; for example, why, when there are sebaceous glands on most areas of the body, is *acne vulgaris* usually limited to the face, back and front of the chest? Many now accept the view that because of an alteration in the ratio between the androgens and œstrogens in the blood stream, hyperkeratosis occurs at the mouths of the sebaceous follicles at the sites of election. This hyperkeratosis leads to the formation of comedones which block the sebaceous glands so that retention cysts are formed. Because the alteration of the androgen/œstrogen ratio is in favour of the androgens, œstrogens and corpus luteum hormones have been advocated for the treatment of *acne vulgaris*.

It is certain that it is unjustifiable to prescribe œstrogens as a routine treatment for this malady. It is my experience that in males, doses in the neighbourhood of 5 to 7 mg. hexœstrol daily are necessary for several weeks if the treatment is to be beneficial, and the effects on the testes may be detrimental. In adolescent girls it is seldom that such doses can be tolerated,

containing zinc undecylenate, 20 per cent., and undecylenic acid, 5 per cent., are effective local applications in the treatment of *fungous infections*. It is probable that these preparations are not more effective than Whitfield's ointment in many cases, whilst in others they seem to be a good deal less efficient, but the undecylenic acid preparations are not irritants, and they have a particular field of usefulness in those many cases in which both a chronic fungous infection and also a chronic dermatitis medicamentosa, caused by continual applications of numerous antiseptics, are present between the toes. Since 1945, other unsaturated fatty acids, e.g. propionic acid, have been used to combat ringworm.

Perlman (1949) has suggested that by the oral administration of undecylenic acid, *psoriasis* may be beneficially influenced. His work requires confirmation, but his views have been studied with interest.

Proprietary preparations.—There has, of course, been a post-war spate of proprietary preparations and, although to discuss but a few of them is indivious, some must be mentioned. Of these, the antihistamine drugs would seem to be the most important, but as readers will have much practical experience of their use, they will not be discussed here.

The work of Pillsbury, Sulzberger and Livingood (1942) had familiarized British dermatologists with "pragmatar" before this ointment was introduced into this country. It is said to contain 3 per cent. of sulphur and salicylic acid with 4 per cent. cetyl tar distillate in a water-miscible base; therefore it may easily be washed out of the scalp. These authors have said that it is "a most useful simple treatment for seborrhœic dermatitis and psoriasis of the scalp . . . Excellent for fungous infections of the groin or feet; pityriasis rosea". My experience of pragmatar is more limited than that of the distinguished Americans from whose work I first learned of the preparation, but certainly for the treatment of *psoriasis*, *dandruff*, and the less acute *seborrhœic eruptions on the scalp*, it is a useful remedy. It is, however, a potent application, and patients must be kept under observation lest the ointment, as occasionally happens, cause desquamation or irritation.

Quinoline derivatives have been used in dermatology for several years. Recently Martin-Scott (1949) and Overton (1949) have advocated the use of "vioform" in the treatment of *impetigo*, folliculitis (particularly *sycosis barbæ*), impetiginized dermatitis and certain *eczematous eruptions*. Overton states that vioform is 5-chloro-7-iodo-8-hydroxyquinoline, and both authors have followed the example of American workers in using both a cream and a soft paraffin ointment, each containing 3 per cent. of the drug. The cream is useful in treating moist conditions. In this concentration vioform is relatively non-irritating and, according to Martin-Scott, does not often cause sensitization.

Martindale's "ether soluble tar powder" has been introduced recently and has many advocates, particularly for the treatment of those *eczematous conditions* in which the use of a powder is preferable to that of a paste.

mayer (1947) who have classified the following maladies as "neuro-dermatoses":

Idiopathic pruritus

(i) Localized (e.g. pruritus of the anus, vulva, scalp)

(ii) Generalized

Neurotic excoriations

Lichenification

Dyshidrosis

Idiopathic chronic urticaria and angioneurotic oedema

Alopecia areata; total and universal alopecia

Lichen planus

Vitiligo

Rosacea

In addition, in certain susceptible individuals, attacks of seborrhœic dermatitis, psoriasis and eczema may be provoked by nervous causes.

Wittkower (1949a) classifies psychosomatic skin diseases broadly into "skin sensations" and "skin manifestations", and an analysis of the list quoted above shows how this conclusion is reached. "Skin manifestations" can be understood as exaggerations and distortions of psycho-physiological skin reactions; dyshidrosis and rosacea are good examples of these abnormalities.

If it is suspected that an eruption is psychological in origin, a careful discussion with the patient is necessary. The object of this discussion is to discover whether psychological disturbances in the patient's life and the onset of his complaint merely coincided or whether they were dynamically interrelated:—

"To prove a casual relationship between disturbing event, emotional disturbance and somatic complaint, it is necessary to show that the disturbing complaint impinged on an infantile neurosis, and that it set in motion mechanisms which otherwise might have led to a psychological disorder. Events which precede the onset of a psychosomatic disorder may be highly dramatic or apparently insignificant, and yet relevant because of their specific effect on the individuals concerned" (Wittkower, 1949b).

The next step is to decide whether or not the case should be passed to a psychiatrist. Sometimes, at this stage, a simple explanation made by the practitioner to the patient will enable him to conquer his disease. In simple words one explains the view expressed by Wittkower (1948):—

"Individuals who are exposed to emotional conflicts, especially in the spheres of self-esteem, aggressiveness, cleanliness and sexuality, may be exposed to situations which intensify these conflicts. This intensification either causes anxiety, feelings of guilt, an urge to confess, or a desire for self-punishment, or it leads to emotional dissociation and flight into illness. Various mechanisms then come into play which are similar to the blush of innocence, the blush of modesty, and to the flush of rage, or to the itching of a person who feels unclean, or the scratching of a person who is confronted by a difficult task".

Often one has to explain that itching may be a sign of suppressed aggression (the patient wounding himself instead of someone whom he

even if arrangements are made to interrupt treatment for several days before each menstrual period. Local treatment would seem to be a more promising method, but if this is used there is no way of ensuring that relatively large quantities will not be absorbed through the skin. The present position therefore seems to be that the proper treatment of acne depends upon a many-sided approach in which factors of diet and habits of life must be regulated, the usual sulphur lotions or sulphur and resorcin pastes prescribed, and the patient instructed in the technique of removal of blackheads and the toilet of the skin. Warren's (1946) suggestion of the use of a rubber sponge for mild suction is valuable. The sponge, loaded with hot water, is pressed against the skin, then allowed to expand by releasing the pressure, the process being repeated rapidly half a dozen times until the sponge is filled with air. It is only when these simple measures have failed that the use of more elaborate methods of treatment with X-rays and endocrine therapy should be considered.

PSYCHIATRY

It is probable that during the next twenty years the greatest advances in dermatology will be due to investigations in biochemistry and psychiatry, but the mention of the latter subject to many practitioners is still a hazardous business. Nevertheless, in probably a third of dermatological cases psychological factors are of importance, although they are not necessarily the sole reasons for the eruption. If, as a result of anxiety, apprehension or other nervous disturbance the skin is affected, there must be some reason why that organ takes precedence over others as the visible site of the mental disturbance. The reason may be found in the theory of "organs of stress". Briefly, this postulates that in all persons nervous stimuli disturb the functions of certain organs more than others. Certain people "feel sick with anxiety", or develop duodenal ulcer because of long-continued mental stress. To have one's bowels turned to water or to suffer from frequency of micturition because of fear or apprehension is an almost normal experience. In these cases the stomach, duodenum, large intestine or bladder are all "organs of stress" which respond physiologically or pathologically to psychological disturbance. In some cases the skin is the organ of stress which bears the brunt of nervous agitation, acting as the canvas on which the perturbation of the mind is painted, or as an organ of relief into which the turbulence of the mind can safely be poured. Much biochemical investigation will be necessary before it will be possible to understand fully how mental stress can cause skin eruptions.

If the reader accepts the view that in certain individuals psychological factors can cause cutaneous symptoms, he may inquire whether there are certain eruptions in which the possibility of such factors should be remembered; the answer to this can be given by quoting Becker and Ober-

ADVANCES IN ORTHOPÆDICS

By PHILIP WILES, M.S., F.R.C.S., F.A.C.S.

Orthopædic Surgeon, Middlesex Hospital.

ORTHOPÆDIC surgery is concerned mainly with long-term problems of function, so that progress is not a sudden affair but a process of evolution taking place over a period of years as the late results of treatment become apparent. The subjects chosen for discussion here therefore illustrate present trends rather than new discoveries.

ARTHROPLASTY OF THE HIP

A diseased joint can be prevented from hurting with certainty only in one way, by stopping all movement at the joint, that is, by performing an arthrodesis. Sometimes this can be done without great interference with function, but often, as at the hip, it results in considerable disability. Although a young person usually tolerates arthrodesis of one hip reasonably well, older people do not adapt themselves so readily, especially if the spine is already arthritic. This is because a stiff hip makes sitting difficult, and the older a person is, the more time he is likely to spend sitting. The present trend in the surgery of the hip is away from arthrodesis towards arthroplasty, and since hip disease, particularly osteoarthritis, is very common, any success in this direction must be welcomed.

Many attempts at arthroplasty have been made in the past but it is only recently that methods have been evolved which are both fairly reliable and applicable to a majority of patients. A surgeon is limited by the quality of the material with which he has to work ; he cannot rejuvenate an elderly man with wasted muscles, but he can nearly always free such a man of pain and make him ambulant, and he can often make a younger person fit to lead an almost normal life. Of the several operations available, the most useful are those associated with the names of Smith-Petersen and Batchelor.

Smith-Petersen's operation makes use of a vitallium cup to "re-bush" the joint. Vitallium is a non-electrolytic metal that remains inert in the body without stimulating a fibrous tissue reaction, as is the case with most other metals. The capsule of the joint is excised, the acetabulum and the head of the femur are reshaped with special gouges and remurs, and a cup of the appropriate size is placed between them. The cup is not fixed and movement takes place on both sides of it, that is, between the acetabulum and the cup, and the head of the femur and the cup. In the course of time the articular surfaces once again become covered with hyaline cartilage.

This operation is now becoming the procedure of choice of a number of surgeons for osteoarthritis of the hip in young, middle-aged and elderly patients. No little experience is required, however, to perform it satis-

wishes to punish or attack), or evidence of a desire for self-punishment, or, in the case of some ano-genital prurites, a masturbatory equivalent.

I have ventured to make this incursion into psychiatry because this article is concerned with advances in treatment; but I well appreciate the difficulties of the practitioner who endeavours to utilize this method. In practice it is often best not to attempt too much oneself but to send the patient at an early stage to a reliable psychiatrist for assessment; such an investigation will often reveal etiological factors of the greatest importance which those interested only in somatic medicine will never discover. Or the psychiatrist will decide that he can do little to assist, and then, relieved of doubt, one has a clear field for one's own activities.

ENVOY

There cannot be a formal summary of an article such as this, but it will be obvious to the reader that on the somatic side I regard recent advances in the treatment of cutaneous tuberculosis as being of the greatest importance, although I have dealt with this matter very briefly so as to have space for a wide review of new measures in somatic therapy. By making an incursion into the realm of psychiatry I have tried to emphasize that dermatological treatment demands a much wider vision and more careful planning than is generally recognized.

References

- Becker, S. W., and Obermayer, M. E. (1947): "Modern Dermatology and Syphilology", 2nd edition, Philadelphia, p. 180.
 Brain, R. T., *et al.* (1948): *Brit. med. J.*, **1**, 723.
 Cornbleet, T. (1948): *J. Amer. med. Ass.*, **138**, 1150.
 Martin-Scott, I. (1949): *Brit. med. J.*, **1**, 837.
 Overton, J. (1949): *Ibid.*, **1**, 840.
 Perlman, H. H. (1949): *J. Amer. med. Ass.*, **139**, 444.
 —, and Irving, L. (1949): *Ibid.*, **140**, 865.
 Pillsbury, D. M., Sulzberger, M. B., and Livingood, C. S. (1942): "Manual of Dermatology", Philadelphia and London, p. 373.
 Shapiro, A. L., and Rothman, S. (1945): *Arch. Derm. Syph., Chicago*, **52**, 166.
 Urbach, E., and Lentz, J. W. (1945): *Ibid.*, **52**, 301.
 Warren, C. (1946): *Med. Pr.*, **216**, 115.
 Wittkower, E. (1948): "Modern Trends in Dermatology" (R. M. B. MacKenna), London, Chap. XI.
 — (1949a): Personal communication.
 — (1949b): "Modern Practice in Psychological Medicine" (J. R. Rees), London, Chap. VII.

appear, in theory, to be immaterial if the transplant be derived from the patient himself or from another human. In the United States of America, and to a much lesser extent elsewhere, bone removed at operation and not required, for example after thoracoplasty, is stored in a "deep freeze" for subsequent use in another patient. Reports of the value of the procedure are conflicting, but should it ultimately prove reliable, there will be a saving both in the extent of the mutilation inflicted on the recipient, and in operative time.

The following are examples of the commoner uses of cancellous grafts:—

Arthrodesis of the hip.—In patients with unilateral osteoarthritis and an already stiff hip, arthrodesis may be the best method of relieving pain. Procedures involving dislocation of the joint are attended by considerable shock, but almost every patient can stand the simpler operation of introducing a tri-fin nail which provides temporary stability, and a sliding graft from the outer table of the ilium which unites rapidly and gives permanent fixation (fig. 1). Immobilization in plaster is unnecessary, but the patient should remain in bed for six weeks; protection by a short spica may be desirable for a while after beginning to walk.

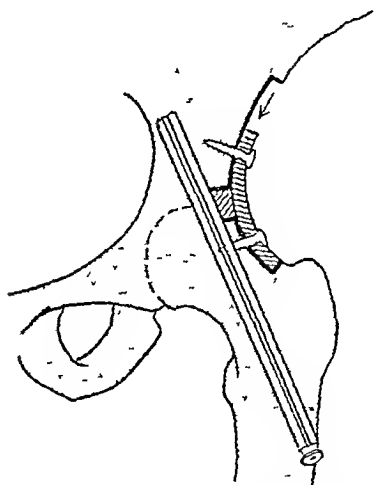


FIG. 1.—Arthrodesis of the hip. Fusion is rapid when a sliding graft from the ilium is used.

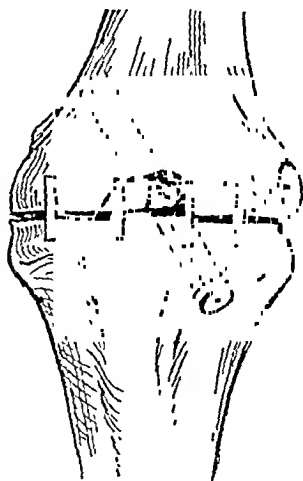


FIG. 2.—Arthrodesis of the knee with inlay grafts of cancellous bone from the lower end of the femur.

Arthrodesis of the knee.—The articular surfaces of the femur and tibia are removed by parallel saw cuts and a tri-fin nail is introduced to give temporary stability; a number of thin grafts cut from the lower end of the femur are fitted into slots made in both bones to ensure rapid fixation (fig. 2). Union ultimately occurs between the whole of the cut surfaces of the bones. A plaster tube extending from ankle to groin is worn for six weeks; weight-



factorily, and it should be carried out only in selected patients. The difficulty is not that it is too severe a procedure for most people to stand, but that success depends largely upon the patient's determined cooperation. The after-treatment is prolonged and involves six weeks in bed followed by six to twelve weeks walking on crutches or wearing a weight-relieving caliper, and during the whole of this time active exercises to maintain the range of movements and build up the muscles must be energetically pursued. Treatment may continue for as long as two years before the best result has been achieved; if this seems a long time for an older person, it must be remembered that the worst of the pain is relieved at once, and that the patient is able to get about fairly well after the first few weeks in bed.

Batchelor's operation differs from the foregoing in that it does not aim at anatomical restoration of the joint. Its chief uses are after failure to secure union of a fractured neck of the femur, and in ankylosis of the hip resulting from rheumatoid arthritis. The operation has two stages, which can be performed at the same time or at separate sessions according to the condition of the patient. The first stage consists in excising the head and neck of the femur, and the second in a subtrochanteric osteotomy of the femur, the fragments being displaced through an angle of 60° and secured to a plate. The lesser trochanter then lodges under the upper lip of the acetabulum and gives some stability, whilst the great trochanter, being bent outwards, provides fair leverage for the gluteal muscles. The patient is confined to bed for about eight to ten weeks while the osteotomy unites, and then wears a weight-relieving caliper for three months. The end-result is a nearly painless hip having moderate stability and a good range of movements, and permitting a fair amount of walking with a marked limp.

THE USE OF CANCELLOUS BONE IN GRAFTING

Until recently, bone used for grafting has been almost exclusively dense cortical bone, removed as a rule from the tibia. A major drawback to the use of dense bone is the time the graft takes to unite with the host and the prolonged period of immobilization therefore necessary. Cancellous bone, usually derived from the pelvis, is now becoming popular because union is more rapid and more certain; in many instances splinting is necessary for no more than six weeks, and sometimes less. Cancellous bone, although it consolidates quickly, has not the strength of cortical bone, and it is probable that when it is used to replace cortical bone it never acquires a comparable density. It is therefore desirable, when strength is necessary, to use both types of bone, the one to give rapid union and the other to provide ultimate strength. This can be achieved either by including the outer table of the ilium in the graft, or, if still greater strength is required, by adding a massive onlay graft from the tibia.

Bone does not live when transplanted from one site to another, but is gradually removed by osteoclasia and replaced by new living bone. It would

gap between the bone ends is packed with cancellous bone. The cancellous bone unites rapidly and external splints can often be removed after eight to ten weeks, permitting the task of loosening stiff joints to be begun. The limb should, however, be protected from rough usage, if necessary by the use of a shield, until the tibial graft has consolidated. Cancellous grafts are especially useful after a compound fracture. It is necessary to wait a long time before a cortical graft can be introduced into an area that has once been infected, but cancellous bone does not sequestrate so readily and can be used much earlier.

CHONDROMALACIA PATELLÆ

It has long been known that the articular cartilage of the patella is liable to degenerate at an early age, but systematic descriptions of the symptoms this causes have appeared only comparatively recently. The typical pathological changes are extremely common and have been found at post-mortem examination in 30 per cent. of bodies of persons eighteen to twenty years of age, the number increasing to over 90 per cent. in middle life. Symptoms, however, are nothing like as common and, although they do occur from time to time in young adults, the chief importance of the disorder is to be found in the part it plays in the etiology of osteoarthritis.

Pathological changes.—The earliest changes are in the central and lower part of the articular cartilage of the patella, which becomes œdematous and loses its glistening appearance. The cartilage splits and flakes and finally becomes detached, leaving an erosion that may be deep enough to extend to the underlying bone. The detached fragments of cartilage sometimes grow and later become ossified to form loose bodies. The degenerative process may stop early before the cartilage has been seriously damaged, but if it progresses until the bone is involved, reactive changes of an osteoarthritic nature take place and osteophytes are formed at the margins of the patella. The osteophytes impinge on the articular cartilage of the femur during movement and this undergoes similar changes, and finally, the corresponding surface on the head of the tibia is involved. It is probable that osteoarthritis of the knee in middle-aged adults develops in this way in a large percentage of patients.

Symptoms are unusual in the early stages before osteoarthritis has supervened, but they do occur, especially in younger people. The onset is often precipitated by a minor injury which causes pain "inside the knee" and an effusion into the joint. The trouble subsides quickly, but it recurs after strenuous exercise and gets progressively worse, until eventually the synovial membrane becomes inflamed and the symptoms continuous. "Pseudo-locking" may occur when there is a partially detached flake of articular cartilage which catches on the femur each time the knee is bent or straightened. The physical signs are not constant but there is often pain

bearing is allowed after three weeks.

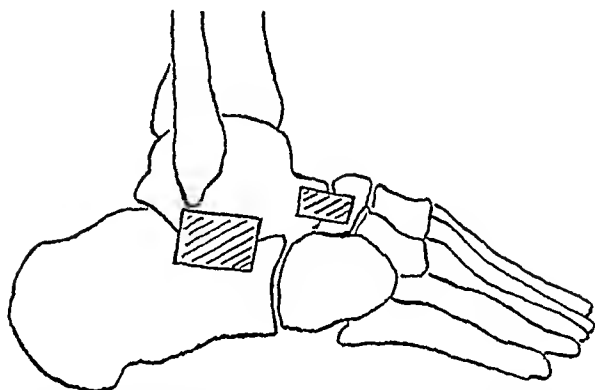


FIG. 3.—Stabilization of the foot by cancellous iliac grafts packed into slots cut across the joints.

Arthrodesis of the foot.—Triple arthrodesis by the classical method is a major undertaking because it means removing the whole of the articular surfaces from the talocalcaneal, talonavicular and calcaneocuboid joints. The same end-result is reached, provided the foot has sufficient mobility to permit its

being moved passively into a good position, by packing cancellous bone tightly into slots cut across these joints (fig. 3). When using this method it is usually unnecessary to fuse the calcaneocuboid joint.

Arthrodesis of the spine.—A new field for surgery is opened by the use of cancellous bone for spinal fusion, because the patient need stay in bed only three weeks instead of spending three months on a plaster bed as was formerly the case. Many of the less severe types of backache can now be offered relief. Temporary stability is given by an H-graft cut from the ilium and fitted between two spinous processes while the spine is in full flexion; it locks firmly in position when the spine is straightened. Permanent fixation is provided by packing cancellous bone into the excised lateral joints, and laying it over the decorticated surface of the laminae (fig. 4).

Ununited fractures.—After removing all fibrous tissue and sclerosed bone, a massive onlay graft from the tibia is screwed to the bone so as to bridge the fracture, and the

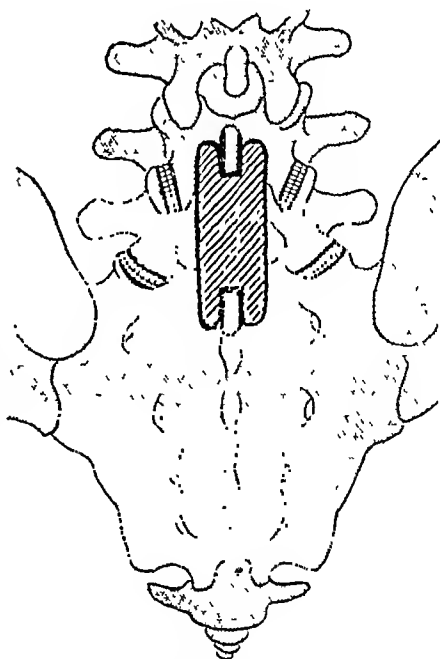


FIG. 4.—Spinal fusion with a graft from the outer table of the ilium and cancellous bone chips.

the

then 30,000 units four-hourly for at least a fortnight. Penicillin can be administered orally to infants under six months old. An abscess, should one form, can be treated by aspirating the pus and replacing it with penicillin in solution, or it can be evacuated through an incision; drilling the bone and similar procedures are not required as a routine.

The course of the disease varies with the virulence of the infection and the stage at which treatment is begun. In the fulminating type, which accounts for most of the fatal cases, the bone infection is overshadowed by the septicæmia, and death may occur before the penicillin is able to exert its effect. The localizing type is fortunately much more common. When treated on the day of onset, or perhaps the next day, the general infection is rapidly controlled, the local condition subsides quickly, no abscess is formed, and the limb soon returns to normal. If treatment is begun later, the infection takes rather longer to control and at least part of the bone is likely to lose its blood supply and die. The organisms have, however, been destroyed, and the dead bone is gradually removed and replaced by new, living bone. The process can be followed radiographically: after about a fortnight the affected area acquires a mottled appearance, then it becomes more translucent as bone is removed, and finally the structure reappears as new bone is formed. When the lower limb is involved, weight-bearing must be avoided until the bone has regained its strength. All patients should therefore remain in bed for about three weeks to give time for necrosis, should it have occurred, to become apparent on the X-rays.

MORTON'S METATARSALGIA

Anterior metatarsalgia, that is, pain in the forefoot, is one of the most ordinary complaints met with in practice but, even though it is so common, there is often confusion as to the cause. The usual type of metatarsalgia, which accounts for perhaps ninety-five out of every hundred cases, arises in the metatarso-phalangeal joints of one or more of the outer four toes. It is really no more than a simple traumatic synovitis caused by repeated minor injuries; it may occur whenever there is a disorder of the foot causing the weight to be carried on the slender, outer joints instead of on the joint of the big toe, which is specially constructed for carrying weight.

Morton's metatarsalgia is an entirely distinct entity and is much less common. It was first described by T. B. Morton during the second half of the last century, and was attributed by him to crushing of the digital branches of the plantar nerves between the metatarsal heads. For a long time afterwards all types of metatarsalgia were included in this category, but eventually it was appreciated that this view of the pathology could not be accepted and it was abandoned. Morton's vivid description of a particular form of metatarsalgia was, however, quite accurate, and the diagnosis was revived when Betts described the true pathology in 1940. He found that when the

on grinding the patella against the femur, and there may be tenderness at the margins of the patella, particularly the lower pole. Ordinary X-rays show no abnormality unless the bone is affected, but after injecting air into the joint it may be possible to demonstrate some irregularity in the outline of the articular cartilage.

Treatment presents a difficult problem because not enough is known about the condition to say how often osteoarthritis is a sequel. In the early stages, operation seems rather drastic and the rational procedure is to protect the joint from injury and rest it for a prolonged period, preferably in plaster. This is hard advice to give an active young man and, as a rule, there is a compromise; a conservative line is followed for a while, but if the symptoms continually recur when the joint is used, it is explored. The operative procedure depends upon the condition found; when only a small area of cartilage is involved, the affected portion should be removed and the edges bevelled off, but with more advanced disease the whole patella should be excised. Obvious osteoarthritic changes are a definite indication for excision of the patella. The functional result after excision of the patella is satisfactory provided after-treatment is good, but it is a somewhat mutilating procedure and in the present state of knowledge should be reserved for the more serious cases.

THE TREATMENT OF ACUTE OSTEOMYELITIS

The introduction of penicillin has had as great an effect on the treatment of acute infection in bone as in other parts of the body, the mortality in acute hæmatogenous osteomyelitis having come down from somewhere in the region of 20 per cent. to 2 per cent. or less, and the subsequent morbidity also has been greatly reduced. The necessity for early diagnosis is, however, at least as great as formerly, because it is only by beginning treatment within a day or so of onset that gross destruction of bone can be prevented. The condition is not very common, but as a rule it can easily be recognized: a child with fever has a pain near one of the large joints, usually the knee, and tenderness on pressure over the metaphysis of the affected bone. These signs are quite sufficient to call for immediate treatment; there are no radiological changes for at least ten days, and there is no need to wait a day or two "to see how things develop". The damage to bone is caused chiefly by necrosis due to the blood supply being interrupted by the inflammatory process; if penicillin is given early enough, this may be prevented, but if treatment is begun late the blood supply to at any rate part of the bone is cut off and penicillin cannot reach it.

General agreement as to the best dosage of *penicillin* has not yet been reached but most surgeons use large quantities. My practice is to give a child an initial injection of 250,000 units, followed by 100,000 units every four hours for forty-eight hours, or until the temperature comes down, and

ADVANCES IN UROLOGY

By M. F. NICHOLLS, C.B.E., M.CHIR., F.R.C.S.

Surgeon, and Surgeon in charge, Genito-Urinary Department, St. George's Hospital.

It is obviously dangerous to assess the value of changes or trends of changes in the treatment of any condition until a period of time has elapsed sufficient to make the assessment significant. For this reason this article describes methods which may seem to some to be established rather than novel. It is not often that small changes of operative technique produce a significant advance, and therefore, in the main, broader principles than these will be discussed.

CHEMOTHERAPY

The most striking advances in urological treatment in recent years have undoubtedly been due directly or indirectly to the effective use of chemotherapy in the prevention, control and cure of urinary infection. The use of the sulphonamides against *B. coli* pyelonephritis and cystitis, and of penicillin against the coccal infections of the urinary tract, is well established. Unfortunately the common demerit and failure of these drugs has also become obvious. Some organisms, particularly *M. tuberculosis*, *B. pyocyaneus* and *B. proteus*, are naturally immune from their effects, whilst insensitivity of others, such as *B. coli*, has increasingly been acquired. It is to deal with such infections that streptomycin and the newer "mycins" have been developed in the United States.

Streptomycin.—In this country we have already some experience of the use of streptomycin, and there are many reports from the United States and elsewhere to help us. It has already been learnt that organisms readily acquire resistance, which may be lasting, to this antibiotic unless they are destroyed by adequate early dosage. Fortunately, urinary infections other than tuberculosis yield rapidly to streptomycin, and a comparatively small dose of from 4 to 5 grammes, given in a period of from thirty-six to forty-eight hours is sufficient, especially in an alkaline urine (Wells, 1949). This small dosage has the added advantage that no serious or lasting toxic effects are likely to follow. It is also probable that, should infection recur, the organisms will not completely have lost their sensitivity. Recurrence of infection will be probable, if not inevitable, if an underlying condition such as stone or obstruction is not dealt with; it has become axiomatic, but nevertheless should be reiterated, that although chemotherapy may modify, it cannot take the place of operative surgery, especially in the event of a mechanical defect.

The sulphonamides are best used in urinary conditions in a mixture such as "sulphatriad", in order that with the differing solubility of the components

typical syndrome was present, and it must be emphasized that this is in only a small proportion of all patients with anterior metatarsal pain, there was always an enlargement of the plantar digital nerve. This observation has been amply confirmed by other surgeons. The swelling involves the nerve immediately proximal to its division into two digital nerves proper, and is about half an inch in length. Microscopic examination shows proliferation of the neurilemma cells and marked interstitial fibrosis. The changes in the nerve are preceded by, and are probably caused by, changes in the plantar digital vessels which accompany them, and it is likely that the spasms of pain are ischæmic in origin.

The outstanding clinical feature is pain which comes on in spasms, there being complete freedom between attacks. The pain starts in the ball of the foot and shoots backwards through the sole and forwards to the tips of a toe or two adjacent toes, usually the third and fourth. It nearly always starts while wearing a shoe, although a few patients have attacks at other times, even when in bed. Relief is obtained by taking off the shoe and rubbing the foot, and the pain is often so severe that this will be done in the street, the sufferer occasionally walking home without a shoe. On examination, the usual signs of ordinary metatarsalgia, such as pain on flexing the affected toe and tenderness on pressure over the metatarso-phalangeal joint, are absent, but the typical pain is reproduced by pressing with a blunt instrument over the distal part of the intermetatarsal space.

The only method of giving relief is to excise the affected portion of the nerve, and the results, when an accurate diagnosis has been made, are so uniformly successful that operation can be recommended without hesitation.

Fig. 1, 2, 3 and 4, are reproduced from "Essentials of Orthopædics" by permission of Messrs. J. & A. Churchill Ltd.

ADVANCES IN UROLOGY

By M. F. NICHOLLS, C.B.E., M.CHIR., F.R.C.S.

Surgeon, and Surgeon in charge, Genito-Urinary Department, St. George's Hospital.

It is obviously dangerous to assess the value of changes or trends of changes in the treatment of any condition until a period of time has elapsed sufficient to make the assessment significant. For this reason this article describes methods which may seem to some to be established rather than novel. It is not often that small changes of operative technique produce a significant advance, and therefore, in the main, broader principles than these will be discussed.

CHEMOTHERAPY

The most striking advances in urological treatment in recent years have undoubtedly been due directly or indirectly to the effective use of chemotherapy in the prevention, control and cure of urinary infection. The use of the sulphonamides against *B. coli* pyelonephritis and cystitis, and of penicillin against the coccal infections of the urinary tract, is well established. Unfortunately the common demerit and failure of these drugs has also become obvious. Some organisms, particularly *M. tuberculosis*, *B. pyocyaneus* and *B. proteus*, are naturally immune from their effects, whilst insensitivity of others, such as *B. coli*, has increasingly been acquired. It is to deal with such infections that streptomycin and the newer "mycins" have been developed in the United States.

Streptomycin.—In this country we have already some experience of the use of streptomycin, and there are many reports from the United States and elsewhere to help us. It has already been learnt that organisms readily acquire resistance, which may be lasting, to this antibiotic unless they are destroyed by adequate early dosage. Fortunately, urinary infections other than tuberculosis yield rapidly to streptomycin, and a comparatively small dose of from 4 to 5 grammes, given in a period of from thirty-six to forty-eight hours is sufficient, especially in an alkaline urine (Wells, 1949). This small dosage has the added advantage that no serious or lasting toxic effects are likely to follow. It is also probable that, should infection recur, the organisms will not completely have lost their sensitivity. Recurrence of infection will be probable, if not inevitable, if an underlying condition such as stone or obstruction is not dealt with; it has become axiomatic, but nevertheless should be reiterated, that although chemotherapy may modify, it cannot take the place of operative surgery, especially in the event of a mechanical defect.

The sulphonamides are best used in urinary conditions in a mixture such as "sulphatriad", in order that with the differing solubility of the components

the danger of massive crystallization should be avoided. Sulphatriad, penicillin, and streptomycin are synergic in their action and in no way antagonistic. Thus it is sensible and practical to use all three together, especially in the cure or prevention of the mixed infections so commonly found in the urinary tract.

STREPTOMYCIN IN TUBERCULOSIS

Urinary tuberculosis presents a different problem. To be effective, streptomycin must be given in larger dosage and over a long period (three to six months) so that the serious toxic effects of the drug commonly result. Its precise rôle in the treatment of renal tuberculosis has yet to be established. Some urologists claim that in the majority of cases streptomycin should supplant surgery. My own experience, admittedly limited, and that of many others, does not support this extreme view; many results over a long period must be assessed before the matter can finally be decided. There is no doubt that when the main focus has been eradicated, residual tuberculous cystitis responds satisfactorily, and there is a good case for the administration of streptomycin for a limited period before and after a nephrectomy for renal tuberculosis. It may also be tried in bilateral cases or when a remaining solitary kidney is involved. The position appears to be the same in the treatment of genital tuberculosis. Streptomycin will not cause disappearance of hard epididymal nodules, but when the main lesion has been removed it will cause residual sinuses to heal rapidly.

PROSTATIC SURGERY

Simple enlargement.—Ever since Freyer invented the transvesical enucleation of the adenomatous prostate, surgeons have been busy in trying to modify or avoid the method. It is indeed a great tribute to the soundness and safety of his operation that even since the coming of chemotherapy the two-stage prostatectomy with open bladder drainage is still used by many as the safest procedure, particularly in bad risks. It nevertheless has its disadvantages in tedious discomfort to the patient and its risks of pulmonary embolus, inevitable infection of the bladder, and the more remote complications, such as bladder-neck obstruction. In the old days deaths from oligæmic shock or uræmia were notorious among elderly men discussing their symptoms and their departed friends in clubs or pubs, and their fearful reluctance was an added stimulus to the surgeon to find a new way. Procedures depending upon the use of hormones and avoiding prostatectomy altogether were tried and found to be completely wanting. In fact, it is fair to say that if hormone treatment succeeds in a case of simple prostatic enlargement it is because the diagnosis is wrong.

Nowadays the trend is towards methods by which the bladder is not opened or is closed at the end of the operation, with early restoration of micturition and the minimum of confinement of the patient to bed. There are two main ways in which this may be done; first, by instrumentation

through the urethra, and secondly, by open operation without opening the bladder, as in the perineal route or the retropubic operation (Millin, 1945), or transvesically but with immediate water-tight closure of the bladder (Harris, 1933; Wilson Hey, 1946). All methods demand hæmostasis and freedom from infection, for hæmorrhage and infection in a closed bladder are more dangerous than in an open one. All methods rely on an indwelling urethral catheter for the immediate postoperative period, and this carries the risk of urethritis and ascending infection. Thus smooth recovery and successful results in all "closed bladder" operations are greatly enhanced by chemotherapy applied prophylactically before and after operation.

Wilson Hey has emphasized the important part played by sepsis in the treatment of prostatic obstruction. He and others claim that the rapid emptying of the chronically distended bladder is a safe procedure provided that it is a strictly aseptic one, and that uræmia, a common sequel in former times, was always the result of acute ascending infection. For the acute or chronic type of obstruction Hey advocates an immediate prostatectomy, instrumentation of any kind before the operation being strictly avoided. His patients are also protected by adequate chemotherapy. Urologists do not universally accept his methods but they owe much to his contention that asepsis in these cases is difficult and most vitally important. There is no doubt that there has been considerable confusion of thought, and therefore of method, in dealing with the distended bladder, and that the procedure of slow decompression has often been used when there was no necessity for it. It is only in cases in which gross distension has been present for a considerable period that ill-effects have been observed from rapid emptying. It seems reasonable in such cases to avoid sudden shocks and changes by taking twenty-four hours or so to empty the bladder. But slow decompression besides being overdone has frequently been ill done. Too slow emptying may leave the bladder as distended as ever, with the catheter tip a potentially infected foreign body; or the catheter may block with clot or come partly out. Such an accident may be unnoticed for some time and distension increase. In any event renewed manipulations will add to the danger of infection and uræmia. In such cases when uræmia is imminent and any interference may precipitate it, an ascending infection is readily acquired and will produce a quick fatality. Such infection is often accompanied by severe hæmorrhage from the inflamed epithelium of the urinary tract. Thus the method of slow decompression should be applied sparingly and only under close skilled supervision. There is no doubt that rapid decompression carries far less risk than was formerly thought, provided that infection is prevented.

Selection of method.—The choice of method of prostatectomy varies within wide limits with the individual urologist. Prostatectomy by the perineal route has never found much favour in this country. Very few surgeons in Britain are "whole hoggers" for endo-urethral prostatectomy, either by the cold punch or by the McCarthy diathermic resectoscope. Most

the danger of massive crystallization should be avoided. Sulphatriad, penicillin, and streptomycin are synergic in their action and in no way antagonistic. Thus it is sensible and practical to use all three together, especially in the cure or prevention of the mixed infections so commonly found in the urinary tract.

STREPTOMYCIN IN TUBERCULOSIS

Urinary tuberculosis presents a different problem. To be effective, streptomycin must be given in larger dosage and over a long period (three to six months) so that the serious toxic effects of the drug commonly result. Its precise rôle in the treatment of renal tuberculosis has yet to be established. Some urologists claim that in the majority of cases streptomycin should supplant surgery. My own experience, admittedly limited, and that of many others, does not support this extreme view; many results over a long period must be assessed before the matter can finally be decided. There is no doubt that when the main focus has been eradicated, residual tuberculous cystitis responds satisfactorily, and there is a good case for the administration of streptomycin for a limited period before and after a nephrectomy for renal tuberculosis. It may also be tried in bilateral cases or when a remaining solitary kidney is involved. The position appears to be the same in the treatment of genital tuberculosis. Streptomycin will not cause disappearance of hard epididymal nodules, but when the main lesion has been removed it will cause residual sinuses to heal rapidly.

PROSTATIC SURGERY

Simple enlargement.—Ever since Freyer invented the transvesical enucleation of the adenomatous prostate, surgeons have been busy in trying to modify or avoid the method. It is indeed a great tribute to the soundness and safety of his operation that even since the coming of chemotherapy the two-stage prostatectomy with open bladder drainage is still used by many as the safest procedure, particularly in bad risks. It nevertheless has its disadvantages in tedious discomfort to the patient and its risks of pulmonary embolus, inevitable infection of the bladder, and the more remote complications, such as bladder-neck obstruction. In the old days deaths from oligæmic shock or uræmia were notorious among elderly men discussing their symptoms and their departed friends in clubs or pubs, and their fearful reluctance was an added stimulus to the surgeon to find a new way. Procedures depending upon the use of hormones and avoiding prostatectomy altogether were tried and found to be completely wanting. In fact, it is fair to say that if hormone treatment succeeds in a case of simple prostatic enlargement it is because the diagnosis is wrong.

Nowadays the trend is towards methods by which the bladder is not opened or is closed at the end of the operation, with early restoration of micturition and the minimum of confinement of the patient to bed. There are two main ways in which this may be done; first, by instrumentation

definitely, and even with a minimum dosage male characteristics tend to disappear and female ones appear. Thus the testes atrophy, the breasts enlarge, and have even been known to develop carcinoma, and the distribution of pubic and other hair is altered. These disadvantages are, however, a small price to pay for the relief of an otherwise incurable disease. Castration seems to enhance the action of oestrogen given by mouth, and if, as is common, the patient is to have an anæsthetic for other procedures, it should be done then. The best and least disturbing and deforming method is to remove the testicular tissue from within the tunica albuginea, which is split and re-sutured.

Diagnostic biopsy.—Carcinoma of the prostate may be obvious clinically on rectal examination. At other times its presence may be suspected but not certain. Although in my experience when there is a suspicion of carcinoma by the feel of the prostate per rectum carcinoma is usually found in the end, it is obviously desirable to have more positive evidence. This can be obtained by endo-urethral resection of part of the prostate, the resected pieces being examined histologically. This is a most satisfactory procedure because sufficient tissue can readily be removed to overcome urinary obstruction, thus obviating the necessity of suprapubic drainage. In a proportion of cases, mainly those with secondary deposits, an increase of the serum acid phosphatase may clinch the diagnosis, but a normal finding does not exclude the presence of carcinoma.

To sum up the treatment: carcinoma of the prostate should when possible be removed surgically. If, as so often, it is beyond the scope of radical surgery, sufficient tissue should be removed by endoscopic resection to relieve obstruction. In either case surgery should be supplemented by hormone treatment, with castration. By such a combination of methods a large proportion of patients although not all, including even those with secondary deposits, will be relieved of symptoms and a proportion will apparently be cured. Hormone treatment, although at a lower level of dosage, should be continued indefinitely, otherwise the carcinoma may recur at any time.

CARE OF THE PARAPLEGIC BLADDER

The war stimulated us to try to solve many surgical problems which, although present in peace time, had not before been faced in such mass. One of these was paraplegia resulting from gun-shot wounds and traffic accidents, and in particular the management of urinary function in such conditions. Improved general treatment has resulted in the long-term survival of many of these patients and gives them hope of a reasonable and useful existence. The urinary treatment must in consequence aim higher than the mere relief of vesical distension and the prevention or postponement of infection ascending to the kidneys. This is, of course, the immediate problem early in the injury or disease, but it is now known that a proportion of these patients can ultimately regain a sufficient degree of bladder control

urologists, however, will agree that this method is suitable for the small fibrous type of simple prostatic obstruction—the type that is most difficult to remove by blunt dissection at open operation. Endo-urethral methods demand special skill and are not without their complications and dangers, such as hæmorrhage and, later, stricture and occasional incontinence.

For the large fleshy prostate most surgeons prefer an open procedure, and it is in the development and more frequent use of one-stage methods which avoid an open bladder postoperatively that progress has been made in recent years. Whatever method is used, retropubic or transvesical, primary or reactionary hæmorrhage occasionally gives trouble and clot retention will sometimes result. This can to a great extent be prevented by washing the bladder at intervals through the indwelling catheter, with small quantities of a 5 per cent. solution of sodium citrate. Should a substantial clot form in spite of this treatment it may often be broken up and removed with a Bigelow's evacuator, whilst as a last resort the bladder must be opened and drained.

When recovery from these "closed" operations is smooth all goes well and patients are up and about and passing urine naturally within a week, but it must be emphasized that the postoperative management demands close supervision by experienced nursing staff and doctors.

In circumstances which are not ideal, and with patients who are poor risks, the two-stage "open bladder" operation may well be the safest.

CARCINOMA OF THE PROSTATE

Opinions vary about the frequency of prostatic cancer but there is no doubt that it is a very common disease. It manifests itself in a number of ways. One way is accidentally at or after the removal of an apparently benign prostatic enlargement. Another is on account of osseous secondary deposits which give rise to sciatica or other root pains. The most common way of all perhaps is by symptoms of "prostatism", indistinguishable from those of a benign enlargement. It is only in the first of these groups that radical surgical removal is likely to be possible, as carcinoma tends to start in the periphery of the gland and quickly to invade surrounding structures. Radiotherapy has never been a success.

Hormone treatment.—Castration as a treatment for prostatism was, of course, advocated many years ago, but the implications of this method were not fully realized and its effect was transitory. Nowadays, however, the use of œstrogen hormones such as stilbæstrol has altered the picture, and even in the presence of metastasis or of advanced urinary obstruction, relief is obtained by a large percentage of patients who are given adequate and prolonged dosage of one of these drugs. A minimum of 15 mg. a day by mouth should be given to start with, and if this is not effective the dose may be raised to as high as 60 mg. a day (Fergusson, 1948). Even so, all cases do not respond and such an amount of œstrogen gives many patients nausea and other unpleasant symptoms. The treatment must be continued in-

peritonally, thus avoiding the main immediate postoperative dangers of peritonitis and obstruction.

There are indications that with measures such as these the operation may become more simple and more safe, and have a wider range of use. After a successful transplant, patients suffer extraordinarily little inconvenience, the bowel learning remarkably well to store and control the evacuation of urine. There are numerous urological conditions for which deviation of the urine from the bladder is advantageous, the chief being intractable vesico-vaginal fistula and vesical neoplasm.

VESICAL CARCINOMA

It is unfortunate that it is in this condition that the results of ureteric transplantation are least encouraging. Total cystectomy is itself by no means a lethal procedure but it must be preceded or accompanied by deviation of the ureters, and the results of the operation, although improving, remain poor. Nor has radiotherapy, whether in the form of radium or deep X-rays, hitherto been satisfactory for vesical carcinoma. One of its frequent disadvantages has been the production of an intractable cystitis. There are, however, signs that radiotherapeutic technique for bladder growths is improving and that satisfactory results, for a short period at any rate, are being obtained. A radioactive solution, thorium X, has been tried in cases of widespread papillomas, always potentially if not actually malignant, but has not proved generally to be efficacious. This form of treatment is admittedly in its infancy, and it is hard to predict whether the treatment of the future will be decided by improvements in operative technique or in the field of radiotherapy. There is much room for improvement, especially as vesical growths can be far advanced before serious symptoms are evident. Hæmaturia is by far the most common manifestation, and the importance of immediate cystoscopic examination of all patients who complain of this symptom cannot be overemphasized.

CONCLUSION

The advances in treatment recounted here are those which seem to be of importance and of proved merit. In the "growing edge" of urology are many active and ingenious minds and dexterous hands. Many new methods are in the experimental stage, and some will in course of time pass the test of experience.

References

- Fergusson, J. D. (1948): *Post-grad. med. J.*, 25, 312.
- Harris, S. H. (1933): *Brit. J. Surg.*, 21, 434.
- Hey, Wilson H. (1946): *Brit. med. J.*, 1, p. 757.
- Millin, T. (1945): *Lancet*, ii, 693.
- Riches, E. W. (1943): *Brit. J. Surg.*, 31, 135.
- (1949): *Brit. J. Urol.*, 21, 51.
- Wells, C. A. (1949): *Ibid.*, 21, 68.

and emptying power to enable them to dispense with artificial drainage. This end can best be achieved if treatment is directed towards it from the start. Patients in whom early recovery is expected, and who can be kept under skilled supervision, may be treated by indwelling urethral catheter with or without "tidal drainage", but in most cases drainage by suprapubic cystostomy has usually to be established in the early stages. What must be avoided is a small, contracted, rigid bladder with an opening to the surface low down just above the symphysis. The cystostomy opening must be made high up, at least as high as half-way between the umbilicus and the symphysis, and the track should run obliquely through the abdominal wall. Riches (1943) has invented a special suprapubic catheter which can be introduced blindly and which seems very suitable for these cases. The bladder is kept clean by chemotherapy when necessary, and mechanically by lavage. With recovery in strength and with re-education many of these patients cease to be bedridden, and a fair proportion learn to walk well with supports. It is at this time that the suprapubic opening should, if possible, be closed. "Tidal drainage" through a urethral catheter is then set up. The "tidal" apparatus consists of a reservoir which fills the bladder up to any chosen pressure and then causes it to empty by siphonage. With it, too, measurements of the tone and capacity of the bladder may be recorded in the form of a cystometrogram and give valuable indication as to the progress of the case. Many of the cases develop a fibrous narrowing of the neck of the bladder and this should be enlarged by endo-urethral resection before function can be restored. With such care many patients obtain effective bladder control, automatic in part since normal sensation is wanting, but helped by voluntary action, such as flexing the trunk and applying manual pressure to the suprapubic region.

TRANSPLANTATION OF THE URETERS INTO THE BOWEL

Ureterocolic anastomosis has always been a most hazardous operation. Its immediate risk has been infection of the peritoneal cavity, whilst later, dilatation and ascending infection of the ureters and renal pelvis and calyces has been a frequent cause of failure. Various technical methods of making the actual anastomosis have been developed, and are associated with such great names as Stiles, Coffey and Grey Turner. The last named stated the essential principles, the most important of which is avoidance of twisting, kinking or compression of the ureter. Two measures have contributed towards the success of the operation in recent years. The first is the preparation of the bowel with some such drug as sulphasuxidine so that the ureter is implanted into a relatively sterile field. The second is the use of normal sodium sulphate by intravenous drip in the immediate postoperative period. This drug is a powerful diuretic and is a safeguard against ascending infection, which would be encouraged by a dry ureter. Of recent years Riches (1949) has used a technique by which the anastomosis is carried out extra-

decane, have appeared on the market almost simultaneously this summer after undergoing brief clinical trials (Mushin *et al.*, 1949; Organe, 1949). Both are powerful relaxants, quicker acting and shorter lasting than curare. Decamethonium iodide is not antagonized by the anticholinesterases (as are flaxedil and curarc), but by *pentamethonium iodide* (or "C₅"), which is its simpler homologue, and which is supposed to act by competitive inhibition. Pentamethonium iodide, however, itself causes an autonomic block which may result in a severe fall of blood pressure. Hence it can be said that "C₁₀" is without a safe and effective antidote. *Prostigmin* is undoubtedly an effective antidote both to *d*-tubocurarine and to flaxedil; but *prostigmin* itself has some undesirable side-effects, which cannot always be prevented by atropine. Indeed, it has recently been held that atropine may at first exaggerate the parasympathomimetic effect of *prostigmin*, and one or two unexpected deaths have been recorded which seemed to have been precipitated by the use of *prostigmin* with or without atropine (Clutton-Brock, 1949). However, both flaxedil and decamethonium iodide are short-acting drugs, and if they are used intelligently an antidote should seldom be required.

Erythroidin and quinine.—Other naturally occurring relaxants, such as the erythrina alkaloids and quinine derivatives, have nothing like the potency of curare and the synthetic compounds, and would seem to have no advantages over them.

Although it was in abdominal surgery that muscle relaxants promised most, they have perhaps borne more fruit when put to other uses. They have come to occupy a valuable place in *anæsthesia for thoracic surgery*. With their help, controlled respiration can readily be established and maintained. The surgeon can avail himself of the advantage of the diathermy cautery inside the chest, and the patient can be assured of an active cough reflex before leaving the operating table.

For the softening of convulsions in *electro-convulsive therapy* they have now an established place. They are also much used to facilitate *peroral endoscopies* and tracheal intubation, although for these purposes their use does not command universal support. They are coming to be used, on an increasing scale, for *Cæsarean section*, since they do not readily cross the placental barrier, and by their use the centrally acting narcotic drugs, which *do* enter the fetal circulation, can be reduced to an absolute minimum (Whitacre and Fisher, 1948; Gray, 1948). They have also been used to control the convulsions of *tetanus* and *strychnine poisoning*. In so far as the exhaustion and hypoxia produced by severe convulsions are contributory causes of death in these cases, the use of muscle relaxants is obviously logical; but the margin between controlling the convulsions on the one hand, and paralyzing the respiratory muscles on the other, is so small that the management of these cases presents great difficulty (Adriani and Ochsner, 1947). It is hard to say whether patients who recover with this treatment

ADVANCES IN ANÆSTHESIA

By RONALD WOOLMER, B.M., B.Ch., D.A., F.F.A.R.C.S.

Senior Lecturer in Anæsthetics, University of Bristol; Anæsthetist, United Bristol Hospitals.

To provide satisfactory operating conditions for the surgeon without poisoning the patient still requires skill and judgment; but the more powerful methods and greater variety of techniques now available to the anæsthetist make him better equipped to guard the interests of the patient without sacrificing those of the surgeon.

THE MUSCLE RELAXANTS

The muscle relaxants have become firmly established as tools of the anæsthetist and it is now possible to make an objective assessment of their value. It cannot be said that their use has resulted in the dramatic drop in postoperative morbidity which it was hoped they would produce, and this fact serves to emphasize that postoperative morbidity is less likely to be diminished by the choice of one or other anæsthetic agent than by careful preoperative assessment and preparation, by the meticulous application of whatever anæsthetic technique is decided upon, and by painstaking post-operative surgical and nursing care. It is probable, too, that through unskilled administration of the muscle relaxants, a few patients have died who would otherwise have survived. This underlines the importance of long and careful training for practitioners who are to handle these powerful drugs.

Curare.—Although *d*-tubocurarine chloride remains the most widely used of all the muscle relaxants, as a never-ending stream of papers and reports testifies, its supremacy has recently been challenged by three synthetic products.

"*Myanesin*", the ortho-tolyl ether of glycerol, was introduced as a muscle relaxant two years ago (Mallinson, 1947) and many reports on it have been published (Ballantine, 1948; Griffith and Cullen, 1948). It is not so good a relaxant as curare, and it may at times cause hæmolysis and venous thrombosis. For these reasons it is not widely used in operative surgery. Unlike other synthetic muscle relaxants it is not destroyed in the alimentary canal, and may exert a prolonged effect when given by mouth in the form of an elixir (Berger and Schwartz, 1948). It has been used in this way in the treatment of various spastic states, such as Parkinsonian rigidity, cerebral diplegia, spasm due to osteoarthritis, and similar conditions; and it may be that in this field it will find a useful application.

"*Flaxedil*", a synthetic benzene derivative with three amino groups, and "*C₁₀*" or *decamethonium iodide*, a methylated ammonium derivative of

highly resistant motor fibres—intact. This technique of "differential spinal block" is proving of value in the elucidation of peripheral vascular disorders and other conditions due to autonomic imbalance.

Total spinal analgesia.—The fall in blood pressure resulting from high spinal analgesia, instead of being regarded as a disadvantage, is now deliberately courted to provide the surgeon with an avascular field. Griffiths and Gillies (1948), have been using total spinal analgesia for thoracolumbar sympathectomies for hypertension. The procaine is encouraged to spread headwards up the spinal canal to such a height as to paralyse most of the vasoconstrictors of the trunk and limbs. Blood from the relaxed vessels collects in the dependent legs, and the blood pressure falls to very low and often unrecordable levels. Cerebral anæmia is guarded against by keeping the head low, and the circulating blood is kept well oxygenated. With this technique the field is not obscured by blood, and few vessels need to be secured. Contrary to expectation, reactionary hæmorrhage is rarely encountered.

"Controlled hypotension".—Because the head must be kept low, total spinal analgesia is not suited to cranial surgery, although the removal of vascular brain tumours demands, even more insistently, a relatively bloodless field. This problem has been tackled by the technique of "controlled hypotension" (Hale, 1948). A proportion of the patient's blood is drained off during the early part of the operation, so that his systolic pressure falls to about 60 mm. Hg.

A cannula is inserted into the radial artery, and through this blood is removed or returned as necessary during the operation. When the tumour has been removed and the vessels have been secured the blood is returned to the patient and the wound is closed. This technique facilitates and shortens cranial operations, not only by reducing bleeding, but also by causing the brain to retract, so that there is much more room for manipulation within the cranium.

With this method the brain appears very different from the turgid, congested organ seen with standard techniques; and there is no doubt that controlled hypotension represents a notable advance.

Continuous caudal analgesia for obstetrics, which has had an acknowledged place in the United States for some years, is slowly becoming popular in this country. Its application to angiospastic conditions, which has been developed by Hingson (1947), and has been so convincingly expounded by him in Britain this summer, introduces a great advance in the therapeutic possibilities of anæsthesia. The vasomotor crises of eclampsia and of acute nephritis can quickly be brought under control, and kept under control, by continuous spinal or caudal analgesia. This relaxes the spastic vessels, decreases the venous pressure, and performs a "bloodless phlebotomy" by pooling blood in the periphery. At the same time, if the block is carried high enough, the kidneys and suprarenals can be temporarily denervated. By the catheter technique, the block can be maintained for a week or ten days if necessary, and its height can be adjusted from hour to hour, according to

would not have done so anyway, and we cannot yet be sure that it is a real advance.

The muscle relaxants are coming to be used in the treatment of *spastic conditions*, such as Parkinsonism, cerebral diplegia, and poliomyelitis. It is said that some relaxant drugs, particularly "introcostrin" (a less pure extract of curare than *d*-tubocurarine) and "myancsin" exert a "lissive" action, which means that they can lessen muscle spasm without impairing voluntary muscle power. Under the influence of this lissive action, spastic patients can move their limbs through a wider range than normally, and this greatly enhances the benefit they derive from re-education by physiotherapy (Ransohoff, 1947). It is clearly desirable that such an effect should be prolonged, and attempts have been made to prolong it by incorporating the drug in a slowly absorbable oily base (Schlesinger, 1946). A more promising method would appear to be to give the drug orally. Myanesin, alone of those discussed, can be given in this way, in the form of an elixir, and good results have been reported from its use.

CONDUCTION ANALGESIA

The study of conduction analgesia has seen considerable development recently. It was prophesied that with the coming of the muscle relaxants spinal analgesia would suffer an eclipse. It is true that it is now far less used for abdominal surgery, but developments and refinements in technique have led to its extension in other spheres.

Continuous, or fractional, spinal analgesia was introduced by Lemmon in 1941. He established the possibility of maintaining spinal analgesia for the longest operation with minimal doses of anæsthetic drug. Many advances in the technique of applying this principle have since been made. Tuohy (1944) substituted a very fine, very flexible catheter for the indwelling needle. This enables the needle to be dispensed with, once the puncture of the dura has been made. Moreover, by proper manipulation of the catheter, true segmental anæsthesia can be obtained (Cann, 1948). The catheter can be threaded through a Tuohy spinal needle with its opening directed towards the head. A measured length of catheter is thus passed intradurally alongside the spinal cord until its end comes to lie in the immediate vicinity of the roots to be anæsthetized. If the catheter is made of suitable material, its position can be radiographically controlled. Dilution by cerebrospinal fluid and diffusion are thus reduced to a minimum, and effects can be produced with remarkably small doses.

Sarnoff and Arrowood (1947, 1948) have made use of the fact that fibres conveying different types of sensation have different susceptibilities to locally acting anæsthetic agents. By using sufficiently dilute solutions, such as 0.2 per cent. procaine, it is possible to block fibres carrying sudomotor and vasomotor impulses and sensibility to pinprick, while leaving touch, deep pressure, vibration and position sense—and, of course, the more

undergone successful trials (Gordh, 1949). Its potency is equal to that of procaine, but it is quicker acting and longer lasting, and more stable in solution. It is also an effective surface analgesic.

ANÆSTHESIA IN CARDIAC SURGERY

Anæsthetic and surgical techniques for the correction of congenital and acquired heart defects have advanced together. This branch of surgery presents many difficulties which must be overcome by the anæsthetist. The patients are always gravely handicapped and have to undergo a long, serious and difficult operation, during which an already precarious blood supply may be temporarily further impaired. In spite of the formidable difficulties, the mortality for these operations is now surprisingly low, due in part to increasing surgical skill; in part to better preoperative evaluation; and in part to advances in anæsthetic technique (Rink *et al.*, 1948).

EXPERIMENTAL METHODS

Anæsthesia in the presence of grave cardio-respiratory disorders has set many new problems, and to provide a basis for their solution certain new experimental techniques have been evolved. Blood oxygen saturation can be measured and continuously recorded during anæsthesia by the *oximeter cell* (Millikan, 1942). This is a device which distinguishes photo-electrically between oxygenated and reduced hæmoglobin. Its use has yielded interesting information (McClure, Behrmann and Hartman, 1948). Similarly, Faulconer and Latterell (1949) have been using new physical methods of analysis to sample the air under an "open ether" mask. They found that the application of the mask alone reduced the partial pressure of oxygen in the mixed air under it from 153 mm. to 123 mm. Adding ether caused a further reduction to about 105 mm.

DIAGNOSTIC AND THERAPEUTIC APPLICATIONS

Diagnostic and therapeutic applications of anæsthesia have lately come much to the fore (Woolmer, 1949).

Peripheral vascular disease.—Sympathetic nerve block is coming to play an increasing part in the elucidation of peripheral vascular disease. By performing a temporary, selective, chemical block, it can give an indication of the results to be expected from a surgical sympathectomy. In prolonged vasospasm following trauma or deep thrombosis, sympathetic block can often interrupt a vicious circle and restore the nutrition of the limb.

In the *vasomotor crises* of eclampsia, acute nephritis, acute thyrotoxicosis, and acute pulmonary œdema, prolonged sympathetic block may be life-saving.

The excruciating pain of *causalgia* and phantom limb pain may often be relieved by a series of sympathetic blocks when all other methods have failed (Schumacher *et al.*, 1948).

the response. A hypertensive, eclamptic, comatose, convulsant patient, with acute heart failure and pulmonary œdema, can be rescued within 30 minutes by the skilful application of this technique, which often lowers the blood pressure 100 mm. of mercury, and simultaneously relieves headache and blurred vision, diminishes pulmonary œdema, slows the failing heart, increases renal output, and coincidentally abolishes pain.

APPARATUS

The "hypo-spray".—Few important advances have been made in apparatus. A method of painless intramuscular injection without the use of a needle has been evolved (Hingson, 1949). This is termed the "hypo-spray". The solution is projected as a high velocity jet through an orifice of only three-thousandths of an inch (0.012 mm.). The injection is completely painless in half the cases; the instrument does not require sterilization; and the method is quicker when large numbers of injections have to be given. On the other hand it is expensive, mechanically complex, and unsuited to viscous solutions.

Trilene vaporizers.—Several new vaporizers for trilene have appeared. Trilene (trichlorethylene) is a useful analgesic agent which, because of its portability, has particular advantages in domiciliary midwifery. Attempts to devise a small cheap vaporizer capable of being safely used by midwives on their own responsibility have not yet been completely successful, but work on this is proceeding (Helliwell and Hutton, 1948).

ANÆSTHETIC AGENTS

A new gaseous agent, *cyclobutane*, has undergone preliminary investigation (Krantz *et al.*, 1948). It is the next higher homologue of cyclopropane, and its properties appear to be closely similar to it, although its potency seems to be greater.

A new analgesic drug, known variously as "physeptone", "methadon", "dolophine", "miadone", and "amidone", has been subjected to fairly extensive clinical trials (Kirchhof and David, 1948). It appears to be a better analgesic than morphine when given in similar doses, and to produce undesirable side-effects in about the same proportion of cases. When used in obstetrics it shows a definite tendency to produce foetal respiratory depression (Prescott and Ransom, 1947).

The use of *sodium succinate* to counter the respiratory depression caused by large doses of the barbiturate is becoming an accepted practice (Barrett, 1948). One to three grammes of a 30 per cent. solution of disodium succinate hexahydrate, repeated as necessary, acts as a very powerful respiratory stimulant, and is preferable to the usual analeptics in that it has apparently no side-effects.

A new local analgesic, "*xylocaine*", which is an acetanilide derivative, has

undergone successful trials (Gordh, 1949). Its potency is equal to that of procaine, but it is quicker acting and longer lasting, and more stable in solution. It is also an effective surface analgesic.

ANÆSTHESIA IN CARDIAC SURGERY

Anæsthetic and surgical techniques for the correction of congenital and acquired heart defects have advanced together. This branch of surgery presents many difficulties which must be overcome by the anæsthetist. The patients are always gravely handicapped and have to undergo a long, serious and difficult operation, during which an already precarious blood supply may be temporarily further impaired. In spite of the formidable difficulties, the mortality for these operations is now surprisingly low, due in part to increasing surgical skill; in part to better preoperative evaluation; and in part to advances in anæsthetic technique (Rink *et al.*, 1948).

EXPERIMENTAL METHODS

Anæsthesia in the presence of grave cardio-respiratory disorders has set many new problems, and to provide a basis for their solution certain new experimental techniques have been evolved. Blood oxygen saturation can be measured and continuously recorded during anæsthesia by the *oximeter cell* (Millikan, 1942). This is a device which distinguishes photo-electrically between oxygenated and reduced hæmoglobin. Its use has yielded interesting information (McClure, Behrmann and Hartman, 1948). Similarly, Faulconer and Latterell (1949) have been using new physical methods of analysis to sample the air under an "open ether" mask. They found that the application of the mask alone reduced the partial pressure of oxygen in the mixed air under it from 153 mm. to 123 mm. Adding ether caused a further reduction to about 105 mm.

DIAGNOSTIC AND THERAPEUTIC APPLICATIONS

Diagnostic and therapeutic applications of anæsthesia have lately come much to the fore (Woolmer, 1949).

Peripheral vascular disease.—Sympathetic nerve block is coming to play an increasing part in the elucidation of peripheral vascular disease. By performing a temporary, selective, chemical block, it can give an indication of the results to be expected from a surgical sympathectomy. In prolonged vasospasm following trauma or deep thrombosis, sympathetic block can often interrupt a vicious circle and restore the nutrition of the limb.

In the *vasomotor crises* of eclampsia, acute nephritis, acute thyrotoxicosis, and acute pulmonary œdema, prolonged sympathetic block may be life-saving.

The excruciating pain of *causalgia* and phantom limb pain may often be relieved by a series of sympathetic blocks when all other methods have failed (Schumacher *et al.*, 1948).

Pelvic cancer.—The intractable pain of inoperable pelvic cancer can be relieved by a carefully placed subarachnoid block with alcohol (Greenhill, 1947), or by a caudal block with procaine (Kenny, 1947).

Postoperative pain.—After upper abdominal operations patients tend to lie still and not to cough because moving and coughing hurt. This immobility is a potent cause of postoperative chest complications. Successful attempts have recently been made (McCleery, Zollinger and Lenahan, 1948) to combat this by blocking the lower intercostal nerves at the end of the operation, so that movement is no longer painful in spite of the recent wound.

Intravenous procaine.—The same effect can be obtained by intravenous procaine (Brittain, 1949). One gramme of procaine in 0.1 or 0.2 per cent. solution is run into the vein during a period of a few hours postoperatively. It is hydrolysed in the circulation before it has time to leak out into the normal tissues. But in tissues the vascularity and capillary permeability of which are increased, such as inflamed areas and recent wounds, the procaine rapidly leaves the circulation and comes in contact with the sensory nerve endings involved. A local anæsthetic effect is thus produced precisely where it is needed.

These and other applications of procaine are being developed and used increasingly by anæsthetists.

CONCLUSION

During the last year or so the most important advance in anæsthesia has taken place on a wider front than the elaboration of techniques and the *introduction of new agents*. It has consisted in an enlargement of the scope of the specialty as a whole, and with it has come a change in the relationship of the anæsthetist to his medical and surgical colleagues. Much more is expected of the anæsthetist now than a few years ago. He is learning to make his contribution to the patient's welfare in the ward no less than in the theatre, and the provision of adequate operating conditions for the surgeon is no longer his sole, or even his major, occupation.

To fit himself to assume these greater responsibilities, the anæsthetist has to undergo a much more arduous training than before in the basic and clinical sciences; and the standard of knowledge required for recognition as a specialist in Great Britain has been greatly raised in the past eighteen months. In that period, too, a Faculty of Anæsthetists has been inaugurated in the Royal College of Surgeons of England, whose chief concern is to raise the standard of academic knowledge of anæsthetists throughout the country. There are now two Chairs of Anæsthesia in England, and others may be created before long.

This awakening to the opportunities available to the properly trained clinical anæsthetist is spreading throughout the English-speaking world. In North America great interest is being taken in the subject, although in the

United States there is still an average of only one medically qualified and trained anæsthetist to four hospitals. In Europe, this side of the iron curtain, a great interest is for the first time being taken in anæsthesia as a science, and there is a constant flow of young men to the postgraduate teaching centres in this country.

References

- Adriani, J., and Ochsner, A. (1947): *Surgery*, 22, 509.
 Ballantine, R. I. W. (1948): *Anæsthesia*, 3, 20.
 Barrett, R. H. (1948): *Anesth. & Analges.*, 27, 326.
 Berger, F. M., and Schwartz, R. P. (1948): *J. Amer. med. Ass.*, 137, 772.
 Brittain, G. J. C. (1949): *Anæsthesia*, 4, 30.
 Cann, J. E. (1948): *Anesthesiology*, 9, 288.
 Clutton-Brock, J. (1949): *Brit. med. J.*, i, 1007.
 Faulconer, A., and Latterell, K. E. (1949): *Anesthesiology*, 10, 247.
 Gordh, T. (1949): *Anæsthesia*, 4, 4.
 Gray, T. C. (1948): *Post-grad. med. J.*, 24, 514.
 Greenhill, E. P. (1947): *Brit. med. J.*, ii, 860.
 Griffith, H. R., and Cullen, W. G. (1948): *Anesth. & Analges.*, 27, 232.
 Griffiths, H. W. C., and Gillies, J. (1948): *Anæsthesia*, 3, 134.
 Hale, D. E. (1948): *Anesthesiology*, 9, 498.
 Helliwell, P. J., and Hutton, A. M. (1948): *Anæsthesia*, 3, 176.
 Hingson, R. A., et al. (1947): *Sth. Surg.*, 13, 582.
 — (1949): *Anesthesiology*, 10, 66.
 Kenny, M. (1947): *Brit. med. J.*, ii, 862.
 Kirchof, A. C., and David, N. A. (1948): *Anesthesiology*, 9, 585.
 Krantz, et al. (1948): *Ibid.*, 9, 594.
 McCleery, R. S., Zollinger, R., and Lenahan, N. E. (1948): *Surg. Gynec. Obstet.*, 86, 685.
 McClure, R. D., Behrmann, O. G., and Hartman, F. W. (1948): *Ann. Surg.*, 128, 685.
 Mallinson, F. B. (1947): *Lancet*, i, 98.
 Millikan, G. A. (1942): *Rev. sci. Instrum.*, 13, 434.
 Mushin, W. W., et al. (1949): *Lancet*, i, 726.
 Organe, G. W. S. (1949): *Ibid.*, i, 773.
 Prescott, F., and Ransom, S. G. (1947): *Ibid.*, ii, 501.
 Ransohoff, N. S. (1947): *Bull. N.Y. Acad. Med.*, 23, 661.
 Rink, E. H., et al. (1948): *Guy's Hosp. Rep.*, 97, 48.
 Sarnoff, S. J., and Arrowood, J. G. (1947): *J. clin. Invest.*, 26, 203.
 — (1948): *Surg. Gynec. Obstet.*, 86, 571.
 Schlesinger, E. B. (1946): *Arch. Neurol. Psychiat.*, 55, 530.
 Schumacher, H. B., et al. (1948): *Surg. Gynec. Obstet.*, 86, 76.
 Tuohy, E. B. (1944): *Anesthesiology*, 5, 142.
 Whitacre, R. J., and Fisher, A. J. (1948): *Anesth. & Analges.*, 27, 164.
 Woolmer, R. F. (1949): *Proc. Roy. Soc. Med.*, 42, 12.

Pelvic cancer.—The intractable pain of inoperable pelvic cancer can be relieved by a carefully placed subarachnoid block with alcohol (Greenhill, 1947), or by a caudal block with procaine (Kenny, 1947).

Postoperative pain.—After upper abdominal operations patients tend to lie still and not to cough because moving and coughing hurt. This immobility is a potent cause of postoperative chest complications. Successful attempts have recently been made (McCleery, Zollinger and Lenahan, 1948) to combat this by blocking the lower intercostal nerves at the end of the operation, so that movement is no longer painful in spite of the recent wound.

Intravenous procaine.—The same effect can be obtained by intravenous procaine (Brittain, 1949). One gramme of procaine in 0.1 or 0.2 per cent. solution is run into the vein during a period of a few hours postoperatively. It is hydrolysed in the circulation before it has time to leak out into the normal tissues. But in tissues the vascularity and capillary permeability of which are increased, such as inflamed areas and recent wounds, the procaine rapidly leaves the circulation and comes in contact with the sensory nerve endings involved. A local anæsthetic effect is thus produced precisely where it is needed.

These and other applications of procaine are being developed and used increasingly by anæsthetists.

CONCLUSION

During the last year or so the most important advance in anæsthesia has taken place on a wider front than the elaboration of techniques and the introduction of new agents. It has consisted in an enlargement of the scope of the specialty as a whole, and with it has come a change in the relationship of the anæsthetist to his medical and surgical colleagues. Much more is expected of the anæsthetist now than a few years ago. He is learning to make his contribution to the patient's welfare in the ward no less than in the theatre, and the provision of adequate operating conditions for the surgeon is no longer his sole, or even his major, occupation.

To fit himself to assume these greater responsibilities, the anæsthetist has to undergo a much more arduous training than before in the basic and clinical sciences; and the standard of knowledge required for recognition as a specialist in Great Britain has been greatly raised in the past eighteen months. In that period, too, a Faculty of Anæsthetists has been inaugurated in the Royal College of Surgeons of England, whose chief concern is to raise the standard of academic knowledge of anæsthetists throughout the country. There are now two Chairs of Anæsthesia in England, and others may be created before long.

This awakening to the opportunities available to the properly trained clinical anæsthetist is spreading throughout the English-speaking world. In North America great interest is being taken in the subject, although in the

that no effect was claimed here for any of the various treatments vaunted for tuberculosis in the past. Evaluation also in certain external tuberculous conditions, such as chronic sinuses and tuberculosis of the skin, is not a very difficult matter, and some remarkable results have been achieved by recently discovered drugs. On the whole, however, the remarks on difficulty of evaluation apply to the great majority of tuberculous conditions, whether of the lungs, bones and joints, genito-urinary system, or other organs.

The question has become particularly important since within the past ten years four separate drugs or groups of drugs which have been investigated in the treatment of tuberculosis have appeared to be more effective than any known before: the sulphone group, calciferol, streptomycin, and *para*-aminosalicylic acid. It is very probable that more effective drugs than these will be found. With the tide of new drugs will flow in also many useless ones. Careful evaluation of them is particularly important in the face of public pressure. The combination of chronicity and of great prevalence means that there are at any one time more sufferers from tuberculosis than from any other disease. It gets more publicity than any other disease, and new drugs are publicized often before their value is proven.

Clinical trial.—Two methods of clinical trial have been helpful in assessing results of new therapy. One is the controlled trial, in which a certain number of patients are treated with the drug, whilst an equal number with comparable disease do not have the drug but are similarly treated in other respects. An example of this type of trial is the recent Medical Research Council trial of streptomycin in pulmonary tuberculosis (1948). The other method, less satisfactory but also less difficult, is to treat with the drug in question a number of patients whose progress over three or six months previous to the beginning of treatment with the drug is known, by detailed recorded clinical observation and X-ray films, to have been downward or stationary. These evaluations are considerably complicated by the intervention of other forms of treatment, in particular of collapse therapy, and when these are widely introduced in the trial, a very large number of cases are required to even-out differences before an answer can be reached.

The value of the organized clinical trial is now appreciated to such a degree that many such are in progress at present in this country and in the United States. Apart from the features of a planned investigation, the acceptance of which alone represents a major advance, these trials are characterized by the fact that they are group endeavours, each with clinicians and pathologists in many different centres taking part.

Limitations.—It is useful, before considering the drugs recently discovered, to set out clearly what we should not expect chemotherapy to do in tuberculosis. It cannot remedy extensive destruction; a lung riddled with chronic thick-walled cavities will not be repaired by any chemotherapy, however powerful. Nor can it have any effect on extensive fibrosis and the complications of such a condition. In other words, chemotherapy cannot deal with the mechanical results of destruction and healing in tuberculous

ADVANCES IN THE TREATMENT OF TUBERCULOSIS

By MARC DANIELS, M.R.C.P., D.P.H.

Member of Scientific Staff, Medical Research Council.

APART from advances in the technique of major surgery in tuberculosis of the lung, the outstanding advance in the treatment of tuberculosis in the past years has been the discovery and development of effective chemotherapy. Certain other progress has been made, particularly in the social aspects of tuberculosis, with the establishment of schemes for financial assistance to the patient and his family, and the better understanding of what is required in rehabilitation schemes. On these matters there is now not so much a lack of understanding of the problems as a slowness or inability to solve them because of material difficulties. Important as they are, it is not proposed to deal with them in this article, and the main theme will be the development of chemotherapy. The approach adopted is critical, for in tuberculosis serious consideration of the possibilities and limitations of chemotherapy is essential; the dangers of excessive use are as great as those of ignoring the cases in which chemotherapy may lengthen or actually save life.

EVALUATION OF CHEMOTHERAPY

To evaluate the effect of a new drug in tuberculosis is not an easy task. In an acute infection of short duration it is relatively simple to assess the effect of a drug such as penicillin. Tuberculosis is in the main a chronic disease with an unpredictable course; the course of the disease is dependent upon the resistance of the individual at the time of infection, that resistance being composed of general, genetic and acquired specific factors; and it is dependent upon the conditions of the individual's life during the development of the disease. So little is still known about the relative and absolute importance of these factors that we cannot, and must not, rely, as a basis for the evaluation of a drug, on the prognosis made by any single clinician, however highly qualified he may be. The history of errors in the evaluation of forms of therapy in pulmonary tuberculosis must stand as a constant reminder that a healthy scepticism is indispensable in this subject. The story of gold therapy, the widespread support accorded to it by many eminent clinicians of our time, is only one example.

These remarks must carry a reservation. There are forms of tuberculosis in which any result other than death can be taken as proof of the effectiveness of a drug; such is tuberculous meningitis, and such also, with a few exceptions, is acute miliary tuberculosis. Any treatment resulting in survival of sufferers from these conditions is an effective treatment. It is interesting

Administration of streptomycin elsewhere than in hospital and under expert guidance is not recommended.

Miliary and Meningeal Tuberculosis

Streptomycin therapy has completely changed the severe prognosis of *acute miliary tuberculosis* (Bunn, 1948), and has reduced the mortality to under 50 per cent.; it is in fact in this condition that the most dramatic recoveries are seen. There is rapid improvement in the clinical condition; in most cases clearing of miliary shadows in the lungs begins within two to three months of starting treatment, and there may be complete clearing within six months. Daily treatment should be continued for at least four months. The course of the disease is often complicated by tuberculous meningitis, even while under treatment. The onset of meningitis may be insidious, and if lumbar puncture shows abnormal elements in the cerebrospinal fluid suggestive of meningitis, then intrathecal therapy should be started.

The results of streptomycin treatment of *tuberculous meningitis*, whilst considerably less good than in uncomplicated miliary tuberculosis, are nevertheless remarkable when the usual 100 per cent. mortality of this condition is borne in mind (Medical Research Council, 1948; Cairns and Taylor, 1949). Results reported to date show survivals (in good condition) in between 20 and 40 per cent. of cases. The prognosis is worst in very young children, and worse in patients admitted already comatose or with established gross pareses than in those at an early stage of the disease. Early diagnosis is the most important single prerequisite to success in treatment. In addition to the classical signs of the disease in its early stages, valuable presumptive evidence may be afforded by the results of the tuberculin test and chest radiography, which should both be done in all cases. In the presence of presumptive evidence, including alterations of the cerebrospinal fluid constituents (the most important being a low sugar level), it is not necessary to wait for bacteriological confirmation before starting treatment, although a direct smear of a pre-treatment specimen should be examined for tubercle bacilli and a part of the specimen put up for culture.

Administration of the drug by both intramuscular and intrathecal routes is necessary. Intramuscular treatment should be maintained for at least four months from the onset of meningitis, and in most cases longer courses will be required. Intrathecal treatment should be given daily during the first few weeks; rest periods are beneficial, but further courses of intrathecal injection are probably necessary, depending upon response to treatment. Optimal frequency and duration of intrathecal treatment have not yet been determined.

Improvement of the clinical condition within two weeks of starting treatment is seen in some cases, but in others the clinical response may be delayed for a long period, and the patient remains in an apparently critical condition for several weeks before improvement is obvious. Once improve-

disease. Its function must be to deal with disease in its active phases, to attack the tubercle bacillus and not to repair the ravages wrought by the germ. When a cavity is the result of progressive destruction in diseased tissue, there is little or nothing to be expected from chemotherapy, so far as that local condition is concerned. On the other hand, when a ballooned thin-walled cavity is due to the obstruction in an inflamed bronchus, then it is reasonable to expect closure by effective chemotherapy. Again also, even in a lung with much chronic disease which has been stabilized, a fresh spread of disease which might prove fatal may be controlled by effective chemotherapy.

These points bear repetition. The main weapon against tuberculous disease lies in the body's own defence mechanisms; chemotherapy must serve mainly the purpose of supplementing these defences at a time when they are low or when the bacterial onslaught is particularly heavy.

STREPTOMYCIN

Streptomycin is clinically the most effective of the drugs so far discovered to act against the tubercle bacillus. Convincing proof of its value in certain forms of the disease has been obtained through organized investigations. It is now accepted that in meningeal and miliary tuberculosis, streptomycin provides the most effective treatment so far discovered; in some tuberculous conditions it may be considered a useful adjuvant to other forms of therapy; but does not in any way replace them; in others it is of little or no value.

Administration and dosage.—The drug is best administered by intermittent intramuscular injection. Even when local treatment is found to be effective, streptomycin should in most cases be administered by intramuscular injection also. In adults the dose which probably best combines clinical effectiveness with low toxicity is 1 g. per day. Higher daily doses should probably be used only when the clinical condition is so serious as to warrant taking the risk of toxic effects. In children, the basis of daily dosage usually employed is 10 to 20 mg. per pound of body weight, with a maximum dose of 2 g. in conditions such as meningitis, and of 1 g. in less serious conditions. The daily dose may be given in one or two injections.

Toxicity.—Streptomycin is relatively non-toxic, when compared with most other chemotherapeutic substances used in tuberculosis. However, an important toxic effect is that on the vestibular apparatus. Vestibular disturbance was common with the high dosage previously employed; it is still seen in an appreciable proportion of patients receiving only 1 g. a day, when treatment is continued for more than two weeks. The first symptom of disturbance is giddiness, and this may persist for weeks or months. Caloric reaction may be reduced or lost. Damage may be permanent, and although the patient may learn to compensate, trouble may appear when he is walking in the dark or on uneven ground. A hydrogenated derivative, dihydrostreptomycin, has been found to be less damaging to the vestibular apparatus, but it is not completely devoid of toxic action.

may so improve that his prospects of recovery are increased, or his expectation of life prolonged. Streptomycin does not provide definitive treatment. The benefits to be obtained directly from streptomycin treatment are limited usually to a period not greater than four months, and a first period of improvement may be followed by rapid deterioration. However, patients who have improved may, after streptomycin treatment has stopped, continue to make good progress on their own resources or after initiation of collapse therapy. The limited potentialities of streptomycin treatment even in suitable cases appear to be due to emergence of resistant tubercle bacilli strains. Knowledge of the limited period of the drug's effectiveness makes it essential that it be used at a time in the course of the disease when the greatest benefit can be expected, and that it be integrated into an over-all plan of treatment. In general, it is best to start collapse therapy during or immediately following the streptomycin course.

For thoracoplasty with routine indications, use of streptomycin as a prophylactic is not recommended; it should be reserved for the treatment of spreads when they occur. It is possible, however, that streptomycin treatment may render fit for thoracoplasty a patient whose recent acute lesions would normally contraindicate operation. As a prophylactic in lung resection it appears to be beneficial. Its value is established in the treatment of infected Semm spaces.

Other Forms of Tuberculosis

Laryngeal and tracheobronchial tuberculous lesions respond well to streptomycin treatment, healing occurring in over 50 per cent. of cases. Recent lesions respond best, and the prognosis is also dependent upon the amount of underlying pulmonary disease. A course of three months is usually necessary. There is no advantage in giving streptomycin by inhalation.

Tuberculous ulcers of the oro-pharynx respond dramatically to streptomycin. Sinuses of tuberculous origin heal in a high proportion of cases.

Streptomycin treatment has been tried in many other tuberculous conditions but, unlike the conditions just mentioned, results are difficult to assess. In tuberculosis of bones and joints, of glands, of the genito-urinary system, and in peritonitis, it is not yet known if streptomycin is of real value.

Streptomycin Resistance

A major disadvantage of the drug is that after a period of treatment tubercle bacilli may be found to be resistant to its action. After six to eight weeks' treatment, strains up to several thousand times less sensitive than the original strain are isolated in many cases. Once the patient's tubercle bacilli have lost their sensitivity to streptomycin the change is almost always permanent. Guinea-pigs infected with streptomycin-resistant tubercle bacilli do not respond to treatment.

In an effort to avoid development of drug resistance short courses have been given and various rhythms of dosage have been tried, but so far no

ment has begun to take place, progress may be uninterrupted, with gradual return of the clinical condition to normal in a period of three to six months. With the methods of treatment employed up to the present, however, relapses are frequent, and may occur even after the cerebrospinal fluid has returned to normal. In some relapses the picture is one of fresh breakdown of infection, but in many cases a syndrome of progressive hydrocephalus dominates the picture. Spinal block is a frequent complication. Among the most important elements of prognosis after the initial stages of treatment are the patient's clinical condition, the presence or absence of tubercle bacilli in the cerebrospinal fluid, and the sugar level in the cerebrospinal fluid.

The treatment is so arduous and raises so many problems that it should not be undertaken in the home or in small hospital centres unable to take a large number of such cases. The personal experience acquired in handling many cases in one unit is more valuable than any rule-of-thumb prescription for treatment. Prolonged close supervision is necessary; after a period of not less than six months in the main hospital centre, the patient may be sent for convalescence to an institution where periodic complete examinations can be done.

Pulmonary Tuberculosis

A series of clinical investigations, of which reports have been published within the past two years, has established without doubt that streptomycin is a valuable aid to treatment in certain types of pulmonary tuberculosis (Medical Research Council, 1948; Council on Pharmacy and Chemistry, 1948; Veterans Administration, 1947). The most simple general criteria for selection of patients for streptomycin treatment may be stated as follows:—Pulmonary tuberculosis in which the lesions requiring treatment are of recent development, acute, progressive, and unlikely to benefit from conventional methods of treatment (e.g. bed rest and/or collapse therapy) alone. This definition includes acute broncho-pneumonic tuberculosis, and any rapidly progressive condition in which immediate collapse therapy would be dangerous or impracticable. It includes, in fact, all cases in which collapse therapy is rendered temporarily inadvisable by the presence of acute lesions of recent development which are not responding to bed rest. It equally includes those with acute "spreads" after collapse therapy, and cases with thin-walled cavities in which it is thought that the cavities are partly attributable to bronchial obstruction. Streptomycin is not indicated for patients with lesions which offer a good prospect of responding to conventional methods of treatment alone, nor for patients with chronic fibroid or fibrocaseous lesions or apparently terminal conditions.

When the fresh lesions are not accompanied by areas with gross caseation or destructive change, partial clearing may be expected within four months of starting treatment. There is rarely complete clearing, and in a majority of cases the sputum does not become negative as a result of streptomycin treatment alone. The best that can be hoped is that the patient's condition

oxygen consumption of the tubercle bacillus, Lehmann (1946) investigated derivatives of benzoic acid with the purpose of finding a substance possessing bacteriostatic properties against the tubercle bacillus. *Para*-aminosalicylic acid was found to have marked bacteriostatic power *in vitro*, and to be non-toxic to experimental animals. The treatment of experimental tuberculosis in animals gave definite results, although not as striking as those seen with streptomycin (Feldman *et al.*, 1947).

The drug has been used clinically on an extensive scale in Sweden, and more recently in this country. Enthusiastic reports have been published, regarding in particular the improvement in clinical condition and fall in temperature (Dempsey and Logg, 1947). Although at present there is hardly more clinical evidence in its favour than there was for gold therapy fifteen years ago, it is possible that *para*-aminosalicylic acid may prove a powerful aid in the treatment of tuberculosis. The drug has the advantages of being relatively non-toxic, and of being best administered by mouth. Organized clinical trials are in progress in this country, and it is hoped that they may yield a definite answer.

CALCIFEROL

Apart from streptomycin, the most impressive achievement of chemotherapy in tuberculosis has been with calciferol (vitamin D₂) in *lupus vulgaris*. A series of reports on large numbers of cases by Charpy (1943), Dowling and Osler Thomas (1946), and Feeny (1947), leave no room for doubt of the value of the drug. The main advantage is in the time saved and in the greater ease of treatment than with general and Finsen light. Treatment is increasingly efficacious for nine months. The proportion of cases resistant to treatment (20 per cent.) is, however, the same as it was before the advent of calciferol.

There is considerable variation in tolerance to the drug, and it is doubtful whether there is an optimal dose both effective and non-toxic for all patients. Symptoms of intolerance include nausea, epigastric discomfort, depression and weakness. Severe toxic effects have been reported in some patients. When calciferol is given by mouth an alcoholic vehicle should be used.

Some good results have been claimed also in *tuberculous cervical adenitis* (Wallace, 1946). No good effect has been observed in pulmonary tuberculosis.

CONCLUSIONS

Other drugs besides those described are being investigated; for instance, striking results have been reported in Germany with thiosemicarbazone, but the published reports seen so far are inconclusive. A new antibiotic, neomycin, appears promising. The limitations of chemotherapy, however, should not be forgotten; it is highly improbable that any chemotherapy, however effective, will solve the main tuberculosis problems, even if it should render possible the treatment and cure of the early minimal tuberculous lesions discovered by routine radiography. Orthodox treatment and

conclusive advantage has been shown. It is possible that association with other drugs may be effective, but here again no conclusive evidence is yet available.

In favourable cases, despite the development of drug resistance, the treatment will have provided a respite for the patient, and his defences may become capable of dealing with the remaining disease. In many other cases deterioration sets in following development of drug resistance.

These facts render imperative the careful selection of cases for treatment, and especially the careful choice of the right time for streptomycin, since it may not be possible to give further effective courses. Furthermore, they indicate that the drug should not be used indiscriminately, and in particular not for chronic patients likely to remain sputum-positive, as the public health risks of disseminating drug-resistant tubercle bacilli are considerable.

THE SULPHONES

It is well known that the sulphones exercise a deterrent effect on experimental tuberculosis in animals, but that eradication of the virulent infection is not attained. In man some favourable results have been reported, but the absence of control in clinical trials so far reported makes assessment difficult. The results in any case appear far less favourable than those in the guinea-pig. Adequate dosage is difficult to achieve, because of low tolerance and the risk of toxic symptoms. Two compounds in particular have been reported as effective in recent years: promizole and sulphathione.

Promizole is better tolerated by humans than previously tried compounds such as promin. Preliminary clinical trials of this compound in pulmonary tuberculosis did not indicate any marked superiority over promin (Hinshaw, Feldman and Pfuetze, 1945). However, Lincoln and Kirmse (1949) have reported impressive results with promizole in military tuberculosis: of 7 children with acute generalized military tuberculosis, 5 showed complete recession of X-ray evidence of military tuberculosis, and were alive over two years after the drug was first given. All 5 were still receiving maintenance doses of promizole. The drug is goitrogenic, and has a stimulating effect on secondary sex characteristics. Lincoln and Kirmse have also reported impressive results in the treatment of tuberculous meningitis by streptomycin associated with promizole.

Sulphathione, the value of which in experimental infection has been demonstrated, has been reported in this country to be effective in human tuberculosis (Madigan, 1948). A balanced appraisal by Clay (1948) suggests that the evidence in favour of the drug is sufficient to warrant further trial. The drug has shown no effect in military or meningeal tuberculosis. Toxic reactions to this drug are in some cases severe, and attainment of optimal dosage below toxic level requires full laboratory cooperation.

PARA-AMINOSALICYLIC ACID

Following demonstration that salicylic acid and benzoic acid increase the

ADVANCES IN THE TREATMENT OF CANCER

By SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P.

*Surgeon, Westminster Hospital; Consulting Surgeon, Mount Vernon Hospital
and the Radium Institute.*

ADVANCES in treatment can be estimated with greater accuracy in classified groups of tumours than in the whole range of new growths. In a disease as complex as cancer with so many variables in site, mode of spread, rate of growth and degree of malignancy, advances in treatment do of necessity cover many branches of knowledge and no single method of treatment can claim to be an advance in more than a limited field.

Advances in treatment should be judged by the reduction of mortality and of morbidity. The former results in a prolongation of survival approximating the normal expectation of life; the latter in the nearest approach to a normal anatomical and physiological state. Such advances are not always clearly reflected in statistical studies, as the number of people dying of cancer or mutilated by it depends chiefly upon the incidence of the disease. This shows great increase in certain sites, such as the lung, and diminution in others, such as the uterus; it varies with the age structure of the population as a whole and to a smaller degree with the proportion of males and females. The trend of increased longevity has resulted in an increase in the incidence. For these various reasons the achievement of treatment and the measure of control obtained appear to be less important than they really are. In certain sites early diagnosis is responsible for improved results without an actual advance or improvement in the method of treatment adopted.

Treatment aims at eradication of the tumour, and when this is not possible, at such alteration in its natural course as to render it less malignant. Radical treatment is applicable in a small percentage of cases; palliative treatment is possible in the majority of cases. Advances in treatment have made more progress in palliation than in cure. Such advances have made treatment available to a large group of patients previously untreatable, when the tumour was not accessible to surgery, and in widespread metastasis.

Progress affects all three methods of treatment: surgery, irradiation and chemotherapy. The problems associated with each form of treatment are rendered more difficult by our ignorance of the cause of cancer and hence of its prevention, with the exception of the treatment of the few well-known precancerous states. The choice of the therapeutic measure or combinations of treatments depends upon the natural history of the particular tumour, on a true estimation of the limitations of each method of treatment and, what is perhaps appreciated least of all, the possibility of aggravating the

orthodox preventive measures will remain important for many years to come.

A particular problem which must be mentioned in a review of advances in treatment is that of hospitalization. An acute situation has arisen in this country, in which thousands of beds for tuberculosis are left empty on the grounds that there are no nurses to staff them. The problem has been made more acute by the advances of chemotherapy, since more patients are now amenable to treatment. Waiting lists for entry to sanatoria are growing, and a common waiting period is six months. In the hands of a capable chest physician, a case of pulmonary tuberculosis may be treated at home until a bed becomes available and, in fact, domiciliary treatment has been developed considerably within the past two years. It has been developed *faute de mieux*: even under skilled supervision it is not satisfactory to induce and maintain pneumothorax without the repeated radiological control and other services available in hospital. Many thousands of infective and treatable patients who should be in hospital are at home. A rational attack on the problem would involve opening all the beds available for tuberculosis in a region, distributing the available nurses among them, and supplementing the nursing staff with a sufficient staff of nursing auxiliaries and domestics to provide adequate service. This would involve imagination on the part of administrative nursing staff and a breaking down of the tradition of what constitutes a nursing day. This, plus a modification of ideas on bed rest (successfully demonstrated recently by Stevens [1949]), might help to deal with the present anomalies. These anomalies are so grave as to entail a risk that the tuberculosis rate may rise again because of the increased infection in the home and the lack of adequate care for those diagnosed.

References

- Bunn, P. A. (1948): *Amer. J. med. Sci.*, **216**, 286.
 Cairns, H., and Taylor, M. (1949): *Proc. Roy. Soc. Med.*, **42**, 155.
 Charpy, M. J. (1943): *Ann. Derm. Syph.*, Paris, **3**, 331.
 Clay, M. G., and Clay, A. C. (1948) *Lancet*, **ii**, 180.
 Council on Pharmacy and Chemistry (1948): *J. Amer. med. Ass.*, **138**, 584.
 Dempsey, T. G., and Logg, M. H. (1947): *Lancet*, **ii**, 872.
 Dowling, G. B., and Prosser Thomas, E. W. (1946): *Ibid.*, **i**, 919.
 Feeny, P. J. (1947): *Ibid.*, **i**, 438.
 Feldman, W. H., and Hinshaw, H. C. (1944): *Proc. Mayo Clin.*, **19**, 593.
 ———, Karlson, A. G., and Hinshaw, H. C. (1947): *Ibid.*, **22**, 473.
 Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H. (1945): *Ann. intern. Med.*, **22**, 696.
 ———, ——— (1946): *J. Amer. med. Ass.*, **132**, 778.
 Lehmann, J. (1946): *Lancet*, **i**, 15.
 Lincoln, E. M., and Kirmse, T. W. (1949): *Ibid.*, **i**, 767.
 Madigan, D. G. (1948): *Ibid.*, **ii**, 174.
 Medical Research Council (1948): *Brit. med. J.*, **ii**, 769.
 ——— (1948): *Lancet*, **i**, 582.
 Schatz, A., Bugie, E., and Waksman, S. A. (1944): *Proc. Soc. exp. Biol.*, N.Y., **55**, 66.
 Stevens, H. (1949): *Lancet*, **ii**, 85.
 Veterans Administration (1947): *Amer. Rev. Tuberc.*, **56**, 485.
 Wallace, H. J. (1946): *Lancet*, **ii**, 88.

ADVANCES IN THE TREATMENT OF CANCER

BY SIR STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P.

*Surgeon, Westminster Hospital; Consulting Surgeon, Mount Vernon Hospital
and the Radium Institute.*

ADVANCES in treatment can be estimated with greater accuracy in classified groups of tumours than in the whole range of new growths. In a disease as complex as cancer with so many variables in site, mode of spread, rate of growth and degree of malignancy, advances in treatment do of necessity cover many branches of knowledge and no single method of treatment can claim to be an advance in more than a limited field.

Advances in treatment should be judged by the reduction of mortality and of morbidity. The former results in a prolongation of survival approximating the normal expectation of life; the latter in the nearest approach to a normal anatomical and physiological state. Such advances are not always clearly reflected in statistical studies, as the number of people dying of cancer or mutilated by it depends chiefly upon the incidence of the disease. This shows great increase in certain sites, such as the lung, and diminution in others, such as the uterus; it varies with the age structure of the population as a whole and to a smaller degree with the proportion of males and females. The trend of increased longevity has resulted in an increase in the incidence. For these various reasons the achievement of treatment and the measure of control obtained appear to be less important than they really are. In certain sites early diagnosis is responsible for improved results without an actual advance or improvement in the method of treatment adopted.

Treatment aims at eradication of the tumour, and when this is not possible, at such alteration in its natural course as to render it less malignant. Radical treatment is applicable in a small percentage of cases; palliative treatment is possible in the majority of cases. Advances in treatment have made more progress in palliation than in cure. Such advances have made treatment available to a large group of patients previously untreatable, when the tumour was not accessible to surgery, and in widespread metastasis.

Progress affects all three methods of treatment: surgery, irradiation and chemotherapy. The problems associated with each form of treatment are rendered more difficult by our ignorance of the cause of cancer and hence of its prevention, with the exception of the treatment of the few well-known precancerous states. The choice of the therapeutic measure or combinations of treatments depends upon the natural history of the particular tumour, on a true estimation of the limitations of each method of treatment and, what is perhaps appreciated least of all, the possibility of aggravating the

disease by injudicious treatments. Progress has been made in all three fields: surgery, irradiation and chemotherapy.

SURGERY

Advances in anæsthesia, and the use of antibiotics and of blood transfusion have widened the scope of all surgery, including the surgery of cancer. At present, emphasis is needed on the fact that "bigger" surgery does not always mean "better" surgery and that the magnitude of the operative act must depend as much upon the natural history of the tumour as upon its extent or site. Other factors, such as radiosensitivity, need consideration.

The most important advances in surgery of cancer concern the deep-seated epithelial tumours. Of these, cancer of the lung and of the alimentary canal are the most important. The advances in *thoracic surgery* have rendered pneumonectomy an established procedure and many survivals of ten and more years are on record. Equally, the transthoracic resection of the œsophagus and the combined thoraco-abdominal approach in cases of gastric cancer have made many more cases of gastric and œsophageal cancer amenable to treatment. It is still doubtful if cancer of the stomach can in fact be eradicated by total gastrectomy, even if adjoining viscera such as the spleen and body of the pancreas are removed simultaneously. Nevertheless, the feasibility of multivisceral resections has been shown; and as there is no other method of treatment of cancer of the gastro-intestinal tract, these wide resections constitute the most tangible progress to-day.

More successful and more frequently applicable is the wide-scale *resection of the colon and rectum*. The synchronous abdomino-perineal excision of the rectum is a notable advance in technique. It has increased very considerably the range of operability and offers a good chance of prolonged survival with freedom from disease. Attempts at conservative surgery in rectal cancer with the object of preserving the sphincters and avoiding colostomy are praiseworthy; there is so far no evidence that such conservative operations are of equal value or that they give the same chance against local recurrence. More interesting are the attempts at excision of intra-abdominal lesions which up till quite recently were considered "inoperable".

It is important to note that of all surgical problems "operability" is the most difficult to define. There is a tendency to-day to consider as "operable" tumours which are merely removable. There is evidence that such a conception is fraught with added risks, not only of increased operative mortality, but in fact aggravation of the disease and more rapid and widespread dissemination of the cancer. It is undoubtedly the case in cancer of the breast; it is less obvious in cases of internal cancer and may, in fact, not be so. Conservatism in surgery of abdominal cancer is at present only justifiable if life is likely to be shortened by more heroic measures. Thus all palliative "functional" operations, such as colostomy, short-circuiting, cystostomy, gastrostomy, tracheotomy, must be considered in their true light, namely, that they are merely procedures to delay death from some visceral obstruc-

tion. Attempts at removal of the irremovable cancer are not justifiable; attempts at widening the usefulness of surgery are worthy of all effort. Examples of recent advances in such "greater" surgery are the removal of the head of the pancreas and restoration of the continuity of the bile ducts; transplantation of the ureters with ablation of all or most of the pelvic viscera; removal "*en bloc*" of part of the colon, spleen, pancreas and kidney. The immediate mortality of such procedures is still considerable, about 20 to 30 per cent. Greater experience will no doubt reduce operative mortality. It remains to be seen if the ultimate survivals justify these procedures.

RADIOTHERAPY

The main usefulness of irradiation is in the treatment of accessible epithelial cancer, such as cancer of the skin, mouth, tongue, pharynx and larynx, and of the uterine cervix; in certain stages of cancer of the breast; in the wide group of reticulosis, lymphadenoma, lymphosarcoma, the leukæmias, and in some inaccessible tumours for which surgery is considered unsuitable, such as tumours of the brain and spinal cord and sarcoma of soft tissues. Radiotherapy has determined the classification of tumours according to their response to treatment and has thus added something to the histological study of neoplasms and the interpretation of such histological findings. It has added considerably to the therapeutic measures against cancer. It has as great, although different, limitations as surgery. It has displaced surgery as the first method of treatment in many common lesions. Cancer of the skin can in most cases be treated more effectively by irradiation than by surgery. In the more simple tumours, such as rodent ulcers, permanent regression is obtained in over 90 per cent. of cases; in epithelioma of the skin in 70 per cent.; in cancer of the tongue a 56 per cent. of five-year survivals in gland-free cases is recorded.

Choice of treatment.—Radiotherapy to be effective must be adequate, and to be adequate must be only in the hands of those specially trained in its use. Both X-rays and radium should be available so that the choice of treatment should not be restricted merely by the available apparatus. Even more vital is the appreciation that irradiation should not be used as an excuse for inadequate surgery; equally, irradiation must never be offered as equal in effectiveness to surgery unless it is in fact so.

Certain tumours are better treated by radium, such as cancer of the tongue, larynx and pharynx, and uterine cervix; others are treated in preference by X-rays, for example, all the reticuloses. Irradiation can be used as the sole method of treatment or in association with surgery as a pre- or post-operative measure. Advances in radiotherapy are due chiefly to a greater knowledge of physics, to the development of a new branch of physics—biophysics; to technical advances in the construction of apparatus, and in the realization of the dangers to patient and personnel and in safety measures devised against such dangers.

Apparatus.—The biological effects of irradiation on normal and neoplastic tissues are better understood. The limitations of the usual 200 k.v. X-ray apparatus are now realized. Apparatus of two million volts is available and in use clinically. Apparatus of much higher power, such as the thirty million volt synchrotron, is about to be used clinically. Ten million volt linear-accelerators are under construction. Telcradium units containing 10 grammes of radium are in routine use, and units five and ten times as powerful are within reasonable achievement. The effects of neutrons from a cyclotron have been studied for the past nine years. This vast amount of effort and ingenuity aims at the delivery within the living body of ionizing energy in such a way that the effect on the neoplasm is maximal and the effect on normal tissues minimal.

Results.—The achievement of irradiation in the treatment of cancer can be illustrated by a few figures. A review of 30,000 patients suffering from cancer of the uterine cervix and treated radiologically showed a five-year survival with freedom of disease in nearly 60 per cent. of cases in stage I and in 41 per cent. of cases in stage II. These figures show considerable achievement, especially as the irradiation treatment in these cases is simple, safe, and shows a negligible mortality from treatment. Yet it is equally important to realize that 40 per cent. of these patients (cancer of the cervix, stage I) do not survive five years and that in most of these irradiation has failed to arrest the disease. It is in this group of cases that modern, extensive surgical treatment can achieve further salvage.

RADIOACTIVE ISOTOPES

The advent of the atomic pile, primarily as a war effort aimed at the construction of the atomic bomb, has placed at the disposal of scientists and doctors a source of artificially produced radioactive substances. Most of these are chiefly used as tracers in physiological studies. A few have been used clinically, and of these *radioactive iodine* I^{131} is the best known and is used in the treatment of cancer of the thyroid with skeletal metastasis. The importance of this advance lies chiefly in the fact that radio-active sources can be brought to the tumours by the circulating blood. There is no doubt that skeletal metastasis of thyroid cancer can thus be irradiated, and reports are available of prolongation of life with regression of tumours for periods of several years. The importance of this study is at present not so much in the treatment of a thyroid cancer as in the exploration of a new and different method of irradiating tissues. As the thyroid gland and some types of thyroid cancer have an affinity for iodine, isotopes are used as a source of irradiation. The possibility of using radioactive isotopes in other forms of cancer is naturally being explored. This method of treatment appears to have limited possibilities.

Up till now only very few isotopes have been tried. *Radioactive phosphorus* P^{32} , is of practical interest; given by injection it will result in clinical and hæmatological improvement in polycythæmia vera, and in this condition

it is the method of choice. It is less effective in other types of blood dyscrasias, and the present findings show that in myelogenous and in lymphatic leukaemias of the chronic types results are no better than those by the conventional radiotherapeutic methods. Radioactive phosphorus is of no value in the acute forms of leukaemia; it is less effective in lymphadenoma than X-rays or cytotoxic poisons such as nitrogen mustard.

Of great research interest is *radioactive carbon* C^{14} ; this substance can be used for the synthetic production of other radioactive substances including amino-acids; and such synthetic derivatives are used as tracers in physiological research. It may produce substances with affinities for certain tissues, such as the bone marrow, liver and spleen, and so be used as a source of radioactivity for tissues which show selective absorption of such synthetic compounds.

These substances are now being produced in moderate but increasing quantities in Great Britain and are available through the Medical Research Council for use under experimental conditions. Other isotopes such as *cobalt* are of interest, as they might be used as a substitute for radium, both in the form of needles and eventually for teletherapy. Their shorter active life, about 1 per cent. loss daily, seems a drawback as compared with radium itself.

COMBINED RADIO-SURGICAL METHODS

The limitations of surgery and of radiotherapy dictate the use of a combination of both methods in certain types of tumours. Such combined treatment is well illustrated in cases of *cancer of the breast*. It is generally accepted that in early and favourable cases radical mastectomy is the method of choice, and in the hands of experienced surgeons with sound surgical judgment 70 or more per cent. of five-year survivals is obtained. It is equally well known that in cases with lymph-node invasion, surgery, however radical, fails to arrest the disease in 70 per cent. of cases. It is in this group that a combination of irradiation and surgery is proving of value. Much valuable work has been done on the histology of the breast and lymph glands removed after such preoperative irradiation; these studies show irradiation effects similar to those found in the uterine cervix and the tongue after multiple biopsies during and after radium therapy. Such treatment results in a considerable improvement of the five-year survival periods in stage II cases of cancer of the breast. In more advanced cases irradiation as the sole method of treatment is indicated.

Preoperative radiotherapy is indicated in a small group of other tumours, such as Wilms' tumour, neoplasms of the maxillary antrum, and before amputation of a limb for sarcoma. Attention is drawn to this sequence of treatment as it is as yet not well known and not widely enough practised. In tumours of the maxillary antrum such combined treatment has given excellent results with periods of survival of twenty and more years.

The value of *postoperative irradiation* is different; such treatment pre-

sumes that the operation is incomplete and resolves itself in the treatment of scars or arcs beyond the operation field. Its indications are wide; its value as a preventative of recurrence is very doubtful; as a palliative for postoperative recurrences in suitable cases it plays an important part in the management of the cancer patient.

CHEMOTHERAPY

The medicinal treatment of cancer resolves itself to-day in the experimental use of two different groups of substances: (1) cytotoxic poisons; (2) hormones. These two groups vary fundamentally in their indications, their action on living tissues, and their effect on tumours. Whereas the former is poisonous and is of value only in as much as it is slightly more toxic to the cancerous than to the normal cell, the latter does not attack the cancer cell directly but alters the "internal environment" of the patient and so deprives certain malignant tumours of their aggressive power. The value of both these agents is very great as a research weapon, as a palliative treatment, and as a means of arresting the tumour for a time. It must, nevertheless, be emphasized that they are at present, at their best, means of *temporarily* controlling the natural history of a small group of tumours. None of these substances is curative; their effects are temporary and the best that can be said is that they control certain types of cancer in their final stages and so prolong life.

Cytotoxic poisons.—The best known of these are nitrogen mustard, urethane and folie acid antagonists.

Nitrogen mustard.—Nitrogen mustard (β -chloroethylamine) is given intravenously, 0.1 mg. per kg. of body weight daily, in series of four to six injections spread over ten days. It is highly toxic and produces in most cases immediate vomiting, and occasionally diarrhoea and a fall in blood pressure; it causes subsequently a fall of the white blood count, affecting chiefly the lymphocytes and neutrophils. Repeated series of treatment result in severe anæmia and thrombocytopenia.

Nitrogen mustard has been tried in many types of tumours. Its palliative value is chiefly in the treatment of lymphadenoma in the terminal stages of the disease, when it no longer responds to radiotherapy. In such cases there is at times a most dramatic recovery; it is never lasting and the longest period of remission is a few months. It has been shown to have similar temporary beneficial effects in cancer of the lung. In other types of tumours it is of no value, and although regression of glandular masses in lymphosarcoma has been recorded, this is very exceptional. The effects on the blood count and on the histology of lesions resembles that of irradiation. The compound used is methyl-*bis*(β -chloroethyl)amine. Other mustard derivatives as yet only prepared in research laboratories and used on experimental tumours are to be tried. The search is for a compound which affects the mitosis of abnormal cells and is of lesser toxicity.

Urethane.—This substance is given by the mouth in doses of 2 to 4

grammes daily. It is used in myeloid and lymphatic leukæmia and results in a fall in the total white blood count and regression in the size of the enlarged spleen and lymph glands. Following regression, control of the disease is sometimes obtained by a maintenance dose of 1.5 mg. daily for prolonged periods. Treatment has been continuous in some cases for fifteen months. All clinical manifestations recur on cessation of treatment. The effects of urethane are similar to those of irradiation but can be tried when radiotherapy is no longer effective. It is well known that some cases of chronic leukæmia show either spontaneous or post-irradiation remissions for prolonged periods, and some of the favourable reports may be such remissions. Urethane is an important advance in treatment in chronic cases; it has no effect in acute leukæmias.

Folic acid antagonists.—Of these, aminopterin is available for clinical trial under controlled research conditions. It is a highly toxic substance which even in small doses causes severe leucotoxic effects, widespread hæmorrhages and ulceration of mucous membranes. The indication for its use is in the acute forms of leukæmia. Acute lymphatic, spleno-medullary and monocytic types of leukæmia with a brief expectation of life have been treated and remissions obtained, even in young children. The fall in the blood count is dramatic and immature cells disappear quickly. It is effective merely because of its leucotoxic effect; there seems to be no actual arrest of the disease, which recurs rapidly. Its use is a pointer in the direction of research. Other folic acid antagonists with different molecular structures are being prepared with the object of reducing the toxicity of the drug. Experimentally, reduction in size of tumours in mice has been achieved by its use.

HORMONE THERAPY

The use of hormones in the treatment of cancer is at present applicable solely in cases of cancer of the prostate and cancer of the breast. The control of *prostatic cancer* by stilbæstrol and other synthetic œstrogens is well known. Pain from skeletal metastasis and regression in the size of the prostate with consequent relief of obstructive symptoms are obtained. Periods of regression up to five years are not uncommon. Similar regressions in prostatic cancer follow castration, and some urologists advocate castration as the first remedy and reserve the administration of œstrogens until the later stages of the disease and when skeletal metastases show active growth. The average dose is 15 mg. daily, but vastly greater quantities up to 1000 mg. have been given without undue side-effects, and further periods of regression obtained. The production of synthetic œstrogens by E. C. Dodds, and the researches of Huggins on the physiology of the prostate and the secretion of acid phosphatase, have placed hormones in the forefront of cancer research.

The use of both male and female sex hormones in the treatment of *breast cancer* is of more recent development. The fact that castration was followed by retardation of growth in mammary cancer and its metastasis

has been known for the past fifty years, and was the basis of radiological castration used sporadically ever since. It is, however, only within the last few years that the use of the male sex hormones has been widely investigated. There is overwhelming evidence that hormonal control of cancer of the breast is of real practical value. The most effective substance is testosterone propionate, which is given by injection. Methyl testosterone given by mouth is far less effective. The question of dosage presents difficulties. Variations from 50 to 300 mg. daily are used. With large doses the effects are greater and more lasting. Side-effects, such as hirsutism, change of voice, and enlargement of the clitoris are not proportionate to the dose, and marked masculinization sometimes follows relatively small doses—50 mg. daily—whereas in other patients total doses of 7000 mg. in four to five weeks produce hardly any alteration in the patients' appearance or voice. The use of hormones has given the victim of widespread mammary metastasis an extension of life which was quite unknown before. Skeletal metastases recalcify, pain is relieved, weight increases, and a return to apparently normal health is achieved in some cases. Regression of visceral metastasis, in the pleura, lungs, liver and brain, has also been obtained. Androgens, so dramatically effective in cancer of the breast in females, appear to be useless in cancer of the breast in males. Yet oestrogens are effective in women after the menopause, especially in the older age-groups after the sixth decade. In men, castration does have beneficial effects but not so marked as in women. At present, androgens are the choice in younger patients and in skeletal metastasis; oestrogens in the older age-groups, and in soft tissue recurrence. Complete healing of fungating, ulcerating and bleeding primary growths has been obtained by oestrogens as the sole remedy in old patients. The results are not permanent and the arrest of growth sooner or later is followed by reactivation of the tumours and their further spread, which no longer responds to hormones. The longest period of clinical improvement recorded so far is five years; most cases benefit for eighteen months to three years.

SUMMARY

Surgery, irradiation and chemotherapy have each contributed to the advances in the treatment of cancer. In the life-span of one generation tumours at one time considered inoperable have become amenable to surgical extirpation with a reasonable operative risk and considerable increase in survival rates. Irradiation has replaced surgery in important groups of tumours and has become a great palliative weapon in many types of growths. Medicinal remedies quite unknown twenty years ago have brought relief in some cases of advanced and widespread disease. There is to-day no simple or safe and effective "cure" for cancer; there are, however, many effective ways of controlling it, retarding its spread, altering its course, and so prolonging life and diminishing suffering—an appreciable advance, and therein lies the hope of ultimate victory.

ADVANCES IN THE TREATMENT OF ACUTE INFECTIOUS DISEASES

By WILLIAM GUNN, M.B., F.R.C.P., D.P.H.

Physician, Royal Free Hospital.

PERHAPS the most significant, although inconspicuous, advances in the treatment of the acute infectious diseases have accrued from changes in the diseases themselves, whether caused directly by immunization or indirectly by improvement in the nutritional and social conditions of the more vulnerable sections of the population. Although 1948 witnessed three new health records, with an infant mortality rate of 34 per 1000 live births compared with 41 in 1947 (154 in 1900), a stillbirth rate of 23.1 against 24.1 in the previous year, and a death rate of 10.8 against 12.0, Martin (1949), in a cautious review, hinted that circumstances were perhaps exceptionally favourable and setbacks are inevitable in view of the fluctuating character both of infectious diseases and the populations at risk. The far from infrequent appearance, with high fatality, of infantile gastroenteritis, of poliomyelitis, and of severe whooping-cough, even in the most favourable circumstances, demands a review of methods of prophylaxis as of therapy, whilst occasional outbreaks of enteric fever, *Salmonella* infections and smallpox, although usually circumscribed, bespeak the need for constant vigilance at all levels. Unfortunately, the new Health Service has so far had a disruptive effect on the administration of public health; only the utmost goodwill and cooperation, using all the available agencies, will tide the country over the interim period until adequate clinic, hospital, laboratory and domiciliary facilities have been established, and integrated more closely than hitherto attained or envisaged in the Act.

On the credit side, diphtheria has been virtually eliminated; scarlet fever remains a trivial disease and the period of infectivity can be shortened almost at will with antibiotics; and the infectious complications of childbirth, miscarriage, burns and operation wounds generally have become alike less frequent, less fatal, and less disabling in their effects. The respective parts played by general prophylactic measures and chemotherapy in securing these results may be difficult to access, but there is still room for improvement in the prevention of cross-infection, which may retard recovery or endanger life even in the best hospitals. In the remainder much structural alteration and installation of modern equipment are needed to bring them to a reasonable standard in the light of recent advances in knowledge.

PREVENTION OF CROSS-INFECTION

Although the hazards of the close aggregation of susceptibles have been

has been known for the past fifty years, and was the basis of radiological castration used sporadically ever since. It is, however, only within the last few years that the use of the male sex hormones has been widely investigated. There is overwhelming evidence that hormonal control of cancer of the breast is of real practical value. The most effective substance is testosterone propionate, which is given by injection. Methyl testosterone given by mouth is far less effective. The question of dosage presents difficulties. Variations from 50 to 300 mg. daily are used. With large doses the effects are greater and more lasting. Side-effects, such as hirsutism, change of voice, and enlargement of the clitoris are not proportionate to the dose, and marked masculinization sometimes follows relatively small doses—50 mg. daily—whereas in other patients total doses of 7000 mg. in four to five weeks produce hardly any alteration in the patients' appearance or voice. The use of hormones has given the victim of widespread mammary metastasis an extension of life which was quite unknown before. Skeletal metastases recalcify, pain is relieved, weight increases, and a return to apparently normal health is achieved in some cases. Regression of visceral metastasis, in the pleura, lungs, liver and brain, has also been obtained. Androgens, so dramatically effective in cancer of the breast in females, appear to be useless in cancer of the breast in males. Yet oestrogens are effective in women after the menopause, especially in the older age-groups after the sixth decade. In men, castration does have beneficial effects but not so marked as in women. At present, androgens are the choice in younger patients and in skeletal metastasis; oestrogens in the older age-groups, and in soft tissue recurrence. Complete healing of fungating, ulcerating and bleeding primary growths has been obtained by oestrogens as the sole remedy in old patients. The results are not permanent and the arrest of growth sooner or later is followed by reactivation of the tumours and their further spread, which no longer responds to hormones. The longest period of clinical improvement recorded so far is five years; most cases benefit for eighteen months to three years.

SUMMARY

Surgery, irradiation and chemotherapy have each contributed to the advances in the treatment of cancer. In the life-span of one generation tumours at one time considered inoperable have become amenable to surgical extirpation with a reasonable operative risk and considerable increase in survival rates. Irradiation has replaced surgery in important groups of tumours and has become a great palliative weapon in many types of growths. Medicinal remedies quite unknown twenty years ago have brought relief in some cases of advanced and widespread disease. There is to-day no simple or safe and effective "cure" for cancer; there are, however, many effective ways of controlling it, retarding its spread, altering its course, and so prolonging life and diminishing suffering—an appreciable advance, and therein lies the hope of ultimate victory.

mended by the Ministry of Health. It would appear that the disappearance of clinical diphtheria has already resulted in a low average antitoxic level in adult women, with the result that the offspring are born relatively susceptible compared with pre-war years, and therefore capable of immunization. Titration of the umbilical cord blood, or Schick testing of the child (less accurately of the mother because of the vagaries of placental permeability) could be used to determine whether the child is capable of immunization; according to Vahlquist there is positive interference with the process when the level is 0.1 unit or more but none at 0.02 unit per ml. blood. Bousfield (1949) gave one dose of a specially purified diphtheria toxoid (P.T.A.P.—Parke Davis & Co.) alone and combined with pertussis vaccine at three months, and found 93.5 per cent. Schick negative at one year; but he recommends as a routine safety measure re-inoculation at the age of one year. Combination of antigens tends to cause more reactions than individual inoculations, but the differences are slight, and are more than offset by the reduction in number of injections and usually by a better antibody response. He was convinced that young infants do not experience the same pain or fear of injections exhibited commonly in the later months of infancy. The advantages of combined inoculation have been emphasized by Bell (1948a, b) who found immunity responses to both antigens higher and more persistent, even at less favourable age-groups, than when each was given singly.

The same considerations about the likelihood of giving a positive immunity response apply to inoculation against *smallpox*, which the practitioner should always urge in infancy, although the compulsory Vaccination Acts have been repealed in the National Health Act. It may conveniently be carried out at the same time as the first injection of combined antigens; the multiple pressure method is practically painless and any reaction would have passed off before the vaccination papule appeared. The relative freedom from neurological complications following primary vaccinations in the first year compared with a later age (Conybeare, 1948) and the increased likelihood of susceptible subjects being vaccinated, or coming into contact with virulent smallpox in the course of military service overseas, or of the disease being inadvertently imported as a result of general air transport, are cogent factors in favour of universal vaccination in infancy. A successful "take" is unlikely until after the eighth or ninth month if the mother has been successfully vaccinated during the preceding four or five years, and vaccination in such cases should be deferred to this age.

Tuberculosis.—Until B.C.G. antigen becomes generally available, its use must be restricted to special groups, such as young babies exposed to special risk of infection to tuberculosis, or nurses and medical students who have remained Mantoux-negative reactors. In a recent review Malmros (1948) stressed the superiority of the intradermal method of inoculation (Wallgren, 1948) and its safety under routine conditions. The antigen must be

subjected to much study, both laboratory and field, the problems of prevention cannot be said to be simplified. In a recent Medical Research Council report (1948), incorporating the investigations carried out by a team of workers in this country from the early months of the recent war, a wealth of data, theoretical and practical, is presented on ventilation, air conditioning and sterilization of atmospheres, objects and surfaces, but no master technique emerged which could be put to ready use in planning new hospitals and clinics. Considerations of expense prevent architects and engineers from submitting plans which would inevitably be rejected; in old buildings air-conditioning installations are costly and prone to prove ineffective or may even be dangerous. In their latest pronouncement on the use of ultra-violet irradiation of buildings, especially schools, factories, hospital wards and operating theatres, the council on physical medicine of the American Medical Association (1948) stressed the need for rigid safeguards, both for preventing over-exposure of occupants and for maintaining maximum efficiency under continuous working conditions. The method used in the operating theatre of the Birmingham Accident Hospital (Colebrook and Ross, 1947), whereby sterilized air is blown down over the table to prevent extraneous organisms settling on the operation field, is hardly applicable to individual isolation rooms, unless they are fitted with air locks, as the air from one room may be forced into another, with added risk of subsequent cross-infection. Untreated air, after heating by ceiling or high wall panels, could be removed by negative pressure through the floor with little risk of shunting to other rooms, and with the added advantage that dust, the bugbear of all air-sterilizing techniques, would never rise but be extracted continuously. Dumbell and Lovelock (1949) have recently reported encouraging laundering experiments with handkerchiefs, using octyl cresol as a disinfectant, which is much more efficient than technical white oil, and retains its efficiency for some two weeks. This method could be used for ward and operating theatre gowns, which Duguid and Wallace (1948) found, even when sterilized by heat, to be highly dangerous by harbouring organisms, chiefly *Staphylococcus pyogenes*, liberated from the upper respiratory tract in speaking or coughing, and from the exposed skin by friction. A special design of gown made of dustproof fabric complete with zipp fastener greatly reduced, but did not eliminate, the scatter of organisms. Development of these techniques on a general or routine scale is necessary to make them commercially feasible.

INDIVIDUAL AND GROUP PROPHYLAXIS

Recent investigations by Vahlquist (1949) and by Parish and his colleagues (1949) have shown that active immunization against *diphtheria* is practicable at three to four months in a large majority of subjects, and recommend its adoption at this age instead of at eight to nine months as officially recom-

mended by the Ministry of Health. It would appear that the disappearance of clinical diphtheria has already resulted in a low average antitoxic level in adult women, with the result that the offspring are born relatively susceptible compared with pre-war years, and therefore capable of immunization. Titration of the umbilical cord blood, or Schick testing of the child (less accurately of the mother because of the vagaries of placental permeability) could be used to determine whether the child is capable of immunization; according to Vahlquist there is positive interference with the process when the level is 0.1 unit or more but none at 0.02 unit per ml. blood. Bousfield (1949) gave one dose of a specially purified diphtheria toxoid (P.T.A.P.—Parke Davis & Co.) alone and combined with pertussis vaccine at three months, and found 93.5 per cent. Schick negative at one year; but he recommends as a routine safety measure re-inoculation at the age of one year. Combination of antigens tends to cause more reactions than individual inoculations, but the differences are slight, and are more than offset by the reduction in number of injections and usually by a better antibody response. He was convinced that young infants do not experience the same pain or fear of injections exhibited commonly in the later months of infancy. The advantages of combined inoculation have been emphasized by Bell (1948a, b) who found immunity responses to both antigens higher and more persistent, even at less favourable age-groups, than when each was given singly.

The same considerations about the likelihood of giving a positive immunity response apply to inoculation against *smallpox*, which the practitioner should always urge in infancy, although the compulsory Vaccination Acts have been repealed in the National Health Act. It may conveniently be carried out at the same time as the first injection of combined antigens; the multiple pressure method is practically painless and any reaction would have passed off before the vaccination papule appeared. The relative freedom from neurological complications following primary vaccinations in the first year compared with a later age (Conybeare, 1948) and the increased likelihood of susceptible subjects being vaccinated, or coming into contact with virulent smallpox in the course of military service overseas, or of the disease being inadvertently imported as a result of general air transport, are cogent factors in favour of universal vaccination in infancy. A successful "take" is unlikely until after the eighth or ninth month if the mother has been successfully vaccinated during the preceding four or five years, and vaccination in such cases should be deferred to this age.

Tuberculosis.—Until B.C.G. antigen becomes generally available, its use must be restricted to special groups, such as young babies exposed to special risk of infection to tuberculosis, or nurses and medical students who have remained Mantoux-negative reactors. In a recent review Malmros (1948) stressed the superiority of the intradermal method of inoculation (Wallgren, 1948) and its safety under routine conditions. The antigen must be

properly stored in the cold and used within seven to ten days of manufacture. In the first instance its issue will be restricted to pædiatricians, specialists in tuberculosis, and other approved workers (Ministry of Health statement, 1949).

Similarly, immunization against *scarlet fever*, *typhoid fever* and *tetanus* are reserved for special groups or occasions; doctors, nurses and social workers, inmates of residential institutions for children, or personnel, civil and military, going overseas. For these latter, additional measures, such as inoculation against cholera, dysentery, plague, typhus and yellow fever, may be required according to the country or area.

Although *measles* can be induced in a modified form by the inhalation of virus suspensions attenuated by serial passage in the developing chick embryo (Rake, 1943), and rubella has been transmitted (Anderson, 1949) to selected susceptibles by throat washings of recent cases re-thawed after storing in the frozen state, these measures have not yet passed the experimental stage. Some time must elapse before particular hazards can be eliminated, such as the simultaneous transmission of poliomyelitis or infective jaundice. In the meantime, one is justified in urging that as most infectious diseases due to viruses, notably measles, rubella, mumps and chickenpox, are relatively innocuous in childhood, any occasion for contracting them under suitable conditions should be welcomed, preferably at ages three to five years, and during holiday time at later ages. The social and economic consequences of adults contracting these diseases, and especially of the imposition of quarantine restrictions on contacts, may be serious both to the individual and to industry.

THERAPY

As no therapeutic advance of outstanding importance has been made in recent years, the diseases selected are taken in alphabetical order; as it happens, enteric fever has perhaps been the subject of the most clearly demonstrable progress.

Enteric fever.—The use of antibacterial serum in combating the toxæmia of typhoid fever has been superseded by a combination of penicillin and sulphonamides and, in its turn, by *chloromycetin* (chloramphenicol, synthesized by Parke, Davis & Co.), a drug which for the first time alters in clear-cut fashion the clinical course of this potentially dangerous disease (Woodward *et al.*, 1948). Early administration in adequate dosage naturally gives the best results (Bradley, 1949), but the disease is characteristically protean in its clinical manifestations, and the drug is still excessively expensive. For an average case an initial oral dose of 4 g. is followed by 0.5 g. at four-hourly intervals (or 0.25 g. two-hourly in severe diarrhoeal cases), for five to seven days. The temperature falls rapidly, often accompanied by increased toxæmic effects, presumably from absorption of bacterial products, and may rise again for a day or so, but thereafter progress

is uninterrupted. The dosage interval may be lengthened to the comfort of the patient when constipation is a feature, but reduction of total dosage may lead to return of organisms, even though drug-fastness apparently does not occur.

Another new antibiotic, *aureomycin*, prepared by the Lederle Laboratories from *Streptomyces aureofaciens*, is also active against typhoid organisms, although reports so far have not been entirely encouraging (Finland *et al.*, 1948). Intestinal carriers, due to cholecystitis, apparently still need operative procedures to effect complete elimination, as these drugs do not appear in the biliary passages, although apparently not inactivated by bile. Chronic brucellosis, hitherto difficult to control, responds rapidly to aureomycin (Spink *et al.*, 1948; Galpine, 1949).

Gastro-enteritis: infantile.—Although some strains of salmonella can cause severe and even fatal attacks of gastro-enteritis, and outbreaks have at various times been attributed to faecal streptococci and coliforms, with special serological characters, infantile diarrhoea and vomiting is generally regarded as a virus infection, affecting primarily the upper respiratory tract. Sulphonamides, penicillin, streptomycin and, more recently, polymyxin, have been used not always with controls, and generally with equivocal results; not unnaturally in a disease generally unpredictable in its course and prognosis. Although these organisms are partially suppressed, fresh drug-resistant forms emerge, sometimes in a matter of hours, and multiply rapidly. The dramatic response to parenteral fluids is not always sustained, although nitrogen loss may be made good in some measure by administration of fresh human plasma. Old plasma may cause reactions, presumably due to the impact of the products of protein break-down on an already damaged liver. If fresh plasma is not available, a substitute such as dextran (Thorsen, 1949) may prove safer, supplemented by the essential amino-acids, notably methionine, cystine and tryptophane, which are stable and free from pyrogenic hazards. Estimation of the plasma salts, as of plasma proteins, is an essential guide in the choice and amounts of electrolytes in infusion fluids, particularly in potassium deficiency (Darrow, 1946). Routine estimations of protein fractions, co-enzymes and vitamins, utilizing the known metabolic requirements of selected bacteria for test purposes, may enable the clinician to place the treatment of this disorder on a scientific instead of an empirical basis. Protein synthesis even in health is a complex affair; water depletion and liver damage add materially to its complexity.

Mumps.—Although mumps is a mild disease in children, serious complications may occur after puberty, especially in males. Convalescent serum or the gamma globulin fraction if given early has been found to protect a significant number, but a more decisive action has been claimed (Savran, 1946; Hoyne *et al.*, 1949) for *diethylstilbaestrol*, in doses of 1 to 2 mg., four times daily for five days, or until the parotid swellings have subsided; for orchitis a dosage of 5 mg. four times a day is suggested. An exceptionally

high incidence of mumps meningoencephalitis (Macrae and Campbell, 1949) in the Bristol area, some cases without parotid involvement, is of particular interest in view of reports of encephalomyelitis (Jennings *et al.*, 1949), especially when polioencephalitis is prevalent. Isolation of the virus in monkeys or the fertile egg is necessary to clinch the diagnosis.

Pneumonia: atypical, primary or virus.—Clinically, any form of pneumonia may be imitated by virus pneumonia, particularly influenza, psittacosis and rickettsial infections, which can be ruled out by serological tests. The cold agglutinin test is only positive in about one-third to one-half of the cases, leaving the diagnosis to be made on negative grounds in cases in which the characteristic blood picture (neutropenia) and radiological changes (ground-glass appearance) are absent or equivocal. Although resolution is the rule, it may be protracted, or interrupted by a pyogenic infection which may prove fatal. A series of 13 cases was treated with aureomycin by Schoenbach and Bryer (1949) in which complete resolution followed more rapidly than would normally be expected, although no control cases were observed; after an initial loading dose of 30 to 50 mg. per kg. body weight, 100 to 250 mg. were given orally in capsules every two hours until the patient became afebrile, and thereafter four- to six-hourly for two to three days longer.

Polioomyelitis.—There is hardly need to stress avoidance of operations on the upper respiratory tract during epidemic periods, but Russell (1949) has provided statistical proof to a theory long held that physical exertion predisposes not only to invasion, but determines its extent and severity. The practitioner may be asked about the risk of infection in swimming pools: whilst efficient chlorination as normally practised does inhibit the virus, the presence of much nitrogenous matter may seriously interfere with its virucidal activity, a likely occurrence in hot weather. Sea-bathing is much safer; but again strict avoidance of excessive muscular activity should be enjoined. The care of severer forms, especially of polioencephalitis with bulbar involvement, is best handled in special hospitals with the necessary equipment for resuscitation (*Polioomyelitis Correspondence*, 1949). In a recent case seen by me, which proved fatal shortly after admission, the patient had been treated for pneumonia, and proof of the real nature of the disease was only forthcoming at autopsy. Mild grades of limb paralysis may persist with disabling deformity unless appropriate splintage and physiotherapeutic measures are applied early, preferably at a special centre (Cholmeley, 1949).

Streptococcal infections.—The substitution of penicillin for sulphonamide, both in prevention and treatment, has resulted in rapid clinical resolution and elimination of organisms from the throat, wounds, and the like. It is usual to give 1 mega unit in divided doses (four to six) in the first twenty-four hours, and thereafter procaine penicillin in doses of 300,000 units, once or twice daily for four days. Infected wounds and burns may prove resistant

by virtue of penicillinase production by other organisms, notably *Staphylococcus pyogenes* and coliforms, necessitating the combination of sulphonamides and penicillin, or the use of antibiotics uninfluenced by penicillinase. Penicillin cream with 2 per cent. phenoxetol may serve, but a more stable agent, such as dibromopropamidine, is more likely to be effective.

Whooping-cough.—Both in its immediate threat, especially to infants (over one-half the deaths recorded—875 in England and Wales in 1948—occur under the age of six months), and in its late effects in causing chronic fibrosis and other pulmonary sequelæ, whooping-cough rivals infantile gastro-enteritis and poliomyelitis as the most dreaded disease of childhood. Of the antibiotics active against the causative organism, *Hæmophilus pertussis*, only polymyxin (aerosporin) derived from *B. polymyxa* has been tried on any scale, with results which were suggestive but not decisive (Brownlee and Bushby, 1948; Swift, 1948). As the drug passes the blood-mucous-membrane barrier with difficulty, combined intramuscular and inhalational routes of administration should be used, the latter by means of a Deedon or Collison inhaler, preferably in an oxygen tent. Schwabacher and colleagues (1949) used streptomycin by the inhalational route only, as the drug was not found in the pulmonary secretions when given by intramuscular injection. This may be due to an inhibitory effect of sputum and lung extracts on the drug (Schwabacher, 1948). Excessive sedation (with phenobarbitone usually) or use of high oxygen concentrations may favour pulmonary collapse and accumulation of secretions which, in turn, may lead to pneumonia, fibrosis and bronchiectasis. Changes of posture, the addition of 5 to 10 per cent. CO₂ to the oxygen, and aspiration of secretions through a bronchoscope may avert the worst effects, and re-expansion may be secured weeks or months afterwards with radiological check (Nicholson, 1949). The use of low barometric pressures at high altitudes in aeroplanes in aborting whooping-cough, as eagerly sponsored by the lay press, appears to have little scientific basis; Bergquist (1948) found the measure useless either in flights or in special chambers, and Banks (1949) has given a reserved opinion regarding its place in the low pressure chamber. It is difficult to exclude a psychological effect, particularly in a disease of this kind.

In spite of much effort little progress can be recorded against *influenza*, *febrile catarrh* and the *common cold*. Brewster (1949) found an antihistamine drug of the benadryl type to be active against the common cold, but the trial was not conducted on the stringent lines used with patulin. Dumbell and his co-workers (1949) suggested that octyl cresol may prove effective in preventing spread. Even yet another antibiotic would be a welcome addition to the therapeutic armamentarium against this scourge.

References

- Anderson, S. G. T. (1949): *J. Immunol.*, 62, 29.
Banks, H. S. (1949): *Brit. med. J.*, ii, 226.

high incidence of mumps meningoencephalitis (Maerac and Campbell, 1949) in the Bristol area, some cases without parotid involvement, is of particular interest in view of reports of encephalomyelitis (Jennings *et al.*, 1949), especially when poliomyelitis is prevalent. Isolation of the virus in monkeys or the fertile egg is necessary to clinch the diagnosis.

Pneumonia: atypical, primary or virus.—Clinically, any form of pneumonia may be imitated by virus pneumonia, particularly influenza, psittacosis and rickettsial infections, which can be ruled out by serological tests. The cold agglutinin test is only positive in about one-third to one-half of the cases, leaving the diagnosis to be made on negative grounds in cases in which the characteristic blood picture (neutropenia) and radiological changes (ground-glass appearance) are absent or equivocal. Although resolution is the rule, it may be protracted, or interrupted by a pyogenic infection which may prove fatal. A series of 13 cases was treated with aureomycin by Schoenbach and Bryer (1949) in which complete resolution followed more rapidly than would normally be expected, although no control cases were observed; after an initial loading dose of 30 to 50 mg. per kg. body weight, 100 to 250 mg. were given orally in capsules every two hours until the patient became afebrile, and thereafter four- to six-hourly for two to three days longer.

Polioomyelitis.—There is hardly need to stress avoidance of operations on the upper respiratory tract during epidemic periods, but Russell (1949) has provided statistical proof to a theory long held that physical exertion predisposes not only to invasion, but determines its extent and severity. The practitioner may be asked about the risk of infection in swimming pools: whilst efficient chlorination as normally practised does inhibit the virus, the presence of much nitrogenous matter may seriously interfere with its virucidal activity, a likely occurrence in hot weather. Sea-bathing is much safer; but again strict avoidance of excessive muscular activity should be enjoined. The care of severer forms, especially of poliomyelitis with bulbar involvement, is best handled in special hospitals with the necessary equipment for resuscitation (*Polioomyelitis Correspondence*, 1949). In a recent case seen by me, which proved fatal shortly after admission, the patient had been treated for pneumonia, and proof of the real nature of the disease was only forthcoming at autopsy. Mild grades of limb paralysis may persist with disabling deformity unless appropriate splintage and physiotherapeutic measures are applied early, preferably at a special centre (Cholmeley, 1949).

Streptococcal infections.—The substitution of penicillin for sulphonamide, both in prevention and treatment, has resulted in rapid clinical resolution and elimination of organisms from the throat, wounds, and the like. It is usual to give 1 mega unit in divided doses (four to six) in the first twenty-four hours, and thereafter procaine penicillin in doses of 300,000 units, once or twice daily for four days. Infected wounds and burns may prove resistant

ADVANCES IN NUTRITION

By A. P. MEIKLEJOHN, D.M., B.Sc., M.R.C.P.

Lecturer in Nutrition, Department of Medicine, University of Edinburgh.

IN the years between the world wars nutritional scientists were happily preoccupied, isolating and synthesizing new vitamins. The splendid result—synthetic vitamin pills, apparently possessing the magical properties of food itself—created a profound impression, both on doctors and patients. It took the experience of world war II and after, to demonstrate the limited usefulness of these new agents in the treatment and prevention of nutritional disorders. Whilst there can be no doubt that synthetic thiamine was sometimes life-saving to the inmates of Japanese prison camps (Smith, 1946), synthetic vitamins have proved of little value in correcting the dietary deficiencies that have arisen in Europe as a result of the war. As Sir Jack Drummond (1948) pointed out in his article in *The Practitioner* last year, underfed populations in Europe have lived principally on bread made from long-extraction flour, potatoes and other vegetables. On such a diet "the tendency is for vitamin intakes to be greater, not less, than in ordinary times".

FOOD CONSUMPTION IN BRITAIN

The average British diet, during the war years, contained adequate amounts of the better-known vitamins and other nutrients (Drummond, 1948). The national diet has not altered in any important respect since then, except that more fruit is available. There is therefore no reason for thinking that dietary deficiencies that did not exist during the war are now occurring. That the national diet has not improved much since the war is a source of unhappiness to many, and of rage to not a few. Particularly, visitors to continental Europe are apt to return with invidious comparisons between the food in Britain and the splendid meals that they have enjoyed in countries where the available food is allowed to go to the highest bidder. Here, for better or for worse, Lord Woolton's war-time schemes for spreading the shortages have been continued into the post-war period, so that although the great majority get what should be enough, very few are able to eat *ad lib*.

There are many practitioners to-day who feel, sometimes emotionally, that there must be something wrong with the present British diet because their patients are so often tired and listless; perhaps owing to the lack of some dietary factor at present unknown to nutritional science. That such a factor might exist cannot, of course, be denied; on the other hand the steady post-war improvement in British public health statistics (except for tuberculosis in Scotland (Elliot, 1949)) seems to discount such a possibility. The plain fact is that, on existing knowledge of human nutrition, there is

- Bell, J. A. (1948a): *J. Amer. med. Ass.*, 137, 1009.
 — (1948b): *Ibid.*, 137, 1276.
 Bergquist E. V. V. (1948): *Nordisk. Med.*, 39, 1459.
 Bousfield, G. (1949): *Lancet*, i, 1100.
 Bradley, W. H. (1949): *Ibid.*, i, 869.
 Brewster, J. M. (1949): *Nav. med. Bull., Wash.*, 49, 1.
 Brownlee, G. B., and Bushby, S. R. M. (1948): *Lancet*, i, 127.
 Cholmeley, J. A. (1949): *Post-grad med. J.*, 25, 31.
 Colebrooke, L., and Ross, W. P. O. (1947): *Lancet*, ii, 792.
 Conybeare, E. T. (1948): *Mon. Bull. Min. Hlth Publ. Hlth Lab. Ser.*, 7, 72.
 Council on Physical Medicine, A.M.A. (1948): *J. Amer. med. Ass.*, 137, 1600.
 Darrow, D. C. (1946): *J. Pediat.*, 28, 515.
 Duguid, J. P., and Wallace, A. T. (1948): *Lancet*, i, 845.
 Dumbell, K. R., and Lovelock, J. E. (1949): *Ibid.*, i, 777.
 Finland, H., Collins, H. S., and Paine, T. F. (1948): *J. Amer. med. Ass.*, 138, 946.
 Galpine, I. F. (1949): *Brit. med. J.*, i, 1037.
 Hoyne, A. L., Diamond, J. H., and Christian, J. R. (1949): *J. Amer. med. Ass.*, 140, 662 (see also *The Practitioner*, Sept. 1949, 163, 250).
 Jennings, G. H., Hamilton-Paterson, J. L., and McCallum, F. O. (1949): *Brit. med. J.*, ii, 210.
 Maerae, J., and Campbell, A. M. G. (1949): *Ibid.*, ii, 259.
 Malmros, H. (1948): *Ibid.*, i, 1129.
 Martin, W. J. (1949): *Ibid.*, i, 438.
 Medical Research Council (1948): "Studies in Air Hygiene", H.M. Stationery Office.
 Ministry of Health Statement on B.C.G. (1949): *Brit. med. J.*, i, 625.
 Nicholson, D. P. (1949): *Arch. Dis. Childh.*, 24, 29.
 Parish, H. T., et al. (1949): *Proc. Roy. Soc. Med.*, 42, 402.
 Poliomyelitis Correspondence (1949): *Lancet*, ii, 346.
 Rake, G. (1943): *J. Pediat.*, 23, 376.
 Russell, W. R. (1949): *Brit. med. J.*, i, 465.
 Savran, J. (1946): *Rhode Island med. J.*, 29, 662.
 Schoenbach, E. B., and Bryer, M. S. (1949): *J. Amer. med. Ass.*, 275, 139.
 Schwabacher, H. (1948): *Nature*, 162, 339.
 —, Wilkinson, R. H., and Karran, C. W. C. (1949): *Lancet*, i, 180.
 Spink, W. W., et al. (1948): *J. Amer. med. Ass.*, 138, 1145.
 Swift P. N. (1948): *Lancet*, i, 133.
 Thorsén, G. (1949): *Ibid.*, i, 132.
 Vahlquist, B. (1949): *Ibid.*, i, 16.
 Wallgren, A. J. (1948): *Ibid.*, i, 237.
 Woodward, T. E., Smadel, J. E., et al. (1948): *Ann. intern. Med.*, 29, 131.

parallel increase in world food production. The United Nations Food and Agriculture Organization (1949), of which he was first Director-General, gives a slightly less gloomy prognosis in its latest world forecast compared with a year ago; nevertheless, it is an unhappy probability that practitioners in many parts of the world will have to deal, for the remainder of their professional lives, with patients living on marginal or frankly insufficient calorie intakes. Any future international strife would, of course, make local famines inevitable, and would further intensify the world shortage of calories. For these reasons it is clearly important that the clinical consequences of simple calorie deficiency should be generally known and appreciated.

A recent critical review of the subject (Keys, 1948) summarizes existing knowledge with admirable lucidity and brevity and deserves to be read *in extenso*: it is a summary of a forthcoming book on the subject. The author was director of the classic study, known as the "Minnesota Experiment", in which 32 young men subsisted for six months on a diet providing roughly half their true caloric needs. At the end of this time they had lost, on average, about a quarter of their body weight, and presented the clinical appearance of severe semi-starvation. Elaborate tests of every kind were carried out during the period of underfeeding and for over a year thereafter, during their recovery.

Signs and symptoms.—Keys (1948) describes *the skin* in severe semi-starvation as "thin, dry, scaly, inelastic, pallid and grayish", with slight cyanosis in cold weather. A "splotchy, dirty brownish pigmentation" may appear on the face or elsewhere on the body. The hair is "dull, dry and staring". The eyes look "dull and dead" and the scleræ are unusually avascular. There is usually bradycardia and a reduction in systolic blood pressure. Although fainting and giddiness are common, they are not apparently due to circulatory maladjustment. Physical endurance is markedly reduced.

Eventually dependent *œdema* usually appears. This is not necessarily associated with any marked reduction of plasma protein and is not due to cardiac failure. The principal mechanism seems to be that the extra-cellular fluid volume remains unchanged at its pre-starvation level. This volume becomes relatively excessive as the body becomes wasted. Loss of turgidity in the tissues, through wasting, may also contribute mechanically to the production of *œdema*. The volume of circulating plasma also tends to remain unchanged, but the total mass of red cells is reduced in proportion to the fall in body weight. The result is a moderate *anæmia*, sometimes with slight macrocytosis. When, as so often happens in famines, unsuitable or infected food results in diarrhœa, very marked and often fatal *dehydration* may result.

The heart is markedly reduced in size and the electrocardiogram shows various peculiarities, including low voltages of all deflections. The energy expenditure of the body may be reduced to about half the normal, partly because of reduction in the bulk of actively metabolizing tissue, partly

no objective reason for thinking that normal people, receiving the average diet available in Britain, and the extra supplements allowed to special categories are likely to suffer from malnutrition. The fatigue and lassitude, so often complained of, are much more probably the result of the common monotony and frustration of post-war life, to which the continued lack of free choice in diet certainly contributes. When our present diet is viewed in historical perspective (Kitchin and Passmore, 1949) it must at least be admitted that we are now more fortunate, nutritionally, than many of our forbears.

INDICATIONS FOR PRESCRIBING VITAMIN SUPPLEMENTS

Apart from cases of definite disease in which there is positive reason to suspect malabsorption or defective utilization of foodstuffs, there are at present few rational indications for prescribing extra vitamins in Britain. The exceptions are the infants and young children, pregnant and nursing mothers for whom supplementary sources of vitamins A, D, and C are provided free or elicap, and they should certainly be encouraged to take them. The old and solitary, and those with peculiar eating habits, may also develop vitamin deficiencies; but in such cases it is usually possible to make provision for a better diet, which should be the first consideration in their treatment. In any event, the provision of one or more synthetic vitamins is likely to be but poor treatment for such cases, because they usually suffer from multiple deficiencies that can only be corrected by a full diet.

The prescription of multi-vitamin preparations is undoubtedly an easy solution in cases with non-specific complaints of fatigue and loss of energy; but it should be realized that the benefits, if any, that are likely to accrue, except for the special cases mentioned above, will be psychological rather than physical.

It has been suggested from time to time that additional vitamins, over and above the body's normal needs, may have a tonic or pharmacological effect that is beneficial. Apparent support to this idea has been given by the dramatic therapeutic benefit of massive doses of vitamin D in lupus. But, in fact, this is the only instance known to me in which there is, to date, undisputed evidence that doses of vitamins above the normal needs have therapeutic value. A former report that supplements of thiamine to normally fed children improve their mental agility, has lately been questioned (*Nutrition Reviews*, 1949a).

UNDERFEEDING (CALORIE DEFICIENCY): THE VITAL ISSUE

Possible vitamin deficiencies are now a very minor problem in Britain compared with that of safeguarding the future supply of calories (Drummond, 1948). As Lord Boyd Orr has so tirelessly emphasized, the vital issue to-day is that of an expanding world population without a

The unappetizing nature of the diet, the difficulty of persuading the patient to continue with it, and the necessity for avoiding all other foods, and especially salt, all make it virtually impossible to give this treatment except under the best hospital conditions and with the assistance of a skilled dietitian. The treatment is therefore useless to the general practitioner wanting some way of helping his hypertensive patients.

PROTEINS AND AMINO-ACIDS

There was an excellent review of this subject in *The Practitioner* last year (Thomson, 1948) and another elsewhere (Cuthbertson, 1948). Since there have been few subsequent advances, no detailed discussion is needed here. However, there are a few new topics worth mentioning.

There is undoubtedly a growing interest in the amino-acids: of the 23 known to occur in the body proteins, it has been shown that not more than 9 are "essential", in the sense that a positive nitrogen balance can be maintained in man on purified mixtures of these amino-acids as the sole source of nitrogen (Rose, Haines, Johnson and Warner, 1943). The 9 are: lysine, tryptophane, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine. These are little more than names to practitioners at present, but it may well be that as knowledge of their physiological importance increases, and when some of them become generally available in synthetic form, they may yet become as popular as the vitamins.

Deficiency of methionine results in fatty livers in animals. The whole subject of dietary factors in the causation of liver disease has been reviewed by Himsworth (1947). In cirrhosis of the liver, the value of a nutritious diet, rich in protein and supplemented with vitamin B concentrates, has been amply demonstrated (Patek *et al.*, 1948).

It has recently been shown that tryptophane can substitute for nicotinic acid in the diet (Elvehjem, 1948), thus reviving an old belief (Goldberger and Tanner, 1921) and explaining an old observation that milk, although poor in nicotinic acid, is beneficial in pellagra.

The feeding of glutamic acid has been claimed to improve the mental performance of mongols and other mental defectives, although it is difficult to see how a substance that the body has no apparent difficulty in making for itself can have such an action. A cloud of doubt surrounds this claim (*Lancet*, 1949).

The "animal protein factor".—Evidence from various animal feeding experiments has recently brought to light the fact that there may be some virtue in animal protein that is not present in vegetable protein. For some people in Britain, sighing for pre-war steaks, this seemed like a vindication of their intuitive belief that something is missing from our present diet. The unknown factor in animal protein was subsequently found to occur in good amounts in dried cow dung: a discovery that may have served to

because the body, being lighter, requires less work to move it about, and partly because all voluntary activity is reduced to a minimum. In this way the body achieves some adjustment to the reduced calorie intake. An important warning is that too rapid re-feeding of starving people may place an intolerable strain on the heart and precipitate congestive failure.

One of the most serious effects of severe caloric deficiency is the *change in personality*. Although intellectual capacity is not apparently impaired, apathy, depression and introversion are pronounced. There is a constant craving for food. Hypochondriasis or hysteria may develop. Physical lethargy is combined with heightened irritability, which may be aggravated by noise, since auditory acuity is often more sensitive than normal. The irritability may intensify rather than diminish as re-feeding brings a return of strength, making the people still more difficult to manage. These psychological effects are clearly of the greatest importance in dealing with underfed populations.

DIET AND SUSCEPTIBILITY TO INFECTION

Keys (1948) also reviews some of the recent literature on the largely unsettled question of what part, if any, nutritional factors ordinarily play in determining resistance to infection. It is at least certain that mortality from tuberculosis may be adversely affected by reduced food consumption. Further animal work along the lines of Sengupta and Howie (1949) must be awaited to determine which dietary factors are likely to be particularly concerned.

DIET AND BLOOD PRESSURE: THE RICE DIET

The effect of underfeeding in lowering the systolic blood pressure has been mentioned above. During the siege of Leningrad in 1941-42 there was an apparent fall in the incidence of hypertension, followed by a veritable epidemic of hypertension and coronary deaths when food supplies were restored (Brozek, Chapman and Keys, 1948). There has been a recent revival of interest in nutritional factors in hypertension, particularly in the therapeutic value of low-salt diets, of which Kempner's (1945) "rice diet" (see *The Practitioner*, 1949, 163, 252) has received most attention. This diet consists solely of rice, fruit and sugar. No milk, fat and, above all, salt are permitted. The effect is to provide 2000 Calories daily with only 20 g. of protein, 5 g. of fat and 0.35 g. of sodium chloride. On this regime there is usually some fall in blood pressure, and improvement in retinopathy has been reported (Kempner, 1945). But the treatment is not without danger: impairment of renal function may result (Pines and Perera, 1949). Moreover, it cannot be continued indefinitely because the patients ultimately rebel against the unpalatable diet. No long-term studies have yet been published to show whether or not this treatment has any ultimate beneficial effect on the natural course of the disease.

to me valid. The belief that human nutritional polyneuritis is caused by deficiency of thiamine rests on dubious evidence and a number of mistaken ideas. The perpetuation of this belief helps to keep alive the notion that the simple administration of synthetic thiamine should be an effective cure for nutritional polyneuritis, whereas it is evidently not so (Smith, 1946).

Vitamin E is one of those embarrassing vitamins that has been offered to us in synthetic form before there is any real certainty that it is necessary for man. In case some readers may have been impressed by a recent article in the lay press entitled "A Medical Discovery as great as Insulin", extolling the value of vitamin E in cardiac disease, it may be well to quote an authoritative opinion: "Objective evidence that the drug (vitamin E) provides any real benefit in heart disease is lacking" (*J. Amer. med. Ass.*, 1948).

References

- Anderson, A. Bruce (1946): *The Practitioner*, 156, 376.
 Beattie, J. (1949): *Ibid.*, 163, 236.
 —, Herbert, P. H., and Bell D. J. (1948): *Brit. J. Nutrit.*, 2, 47.
 Brozek, J., Chapman, C. B., and Keys, A. (1948): *J. Amer. med. Ass.*, 137, 1569.
 Cuthbertson, D. P. (1948): *Brit. med. J.*, ii, 731.
 Davidson, L. S. P., and Anderson, I. A. (1947): "A Textbook of Dietetics", 2nd edition, London.
 Drummond, J. (1948): *The Practitioner*, 160, 3.
 Elliot, W. (1949): *Brit. med. J.*, ii, 297.
 Elvehjem, C. A. (1948): *J. Amer. med. Ass.*, 138, 960.
 Food and Agriculture Organization of the United Nations (1949): "World Food Appraisal as of April 1949", Washington.
 Goldberger, J., and Tanner, W. F. (1921): *U.S. Pub. Hlth. Rep.*, 37, 462.
 Himsforth, H. P. (1947): "Lectures on the Liver and its Diseases", Oxford.
 Isbister, J. (1948): *Med. J. Austral.*, 35, 362.
Journal of the American Medical Association (1948): Current Comment, 138, 1159.
 Kempner, W. (1945): *N. Carolina med. J.*, 6, 61, 117.
 Keys, A. (1948): *J. Amer. med. Ass.*, 138, 500.
 Kitchin, A. H., and Passmore, R. (1949): "The Scotman's Food. An Historical Introduction to Modern Food Administration", Edinburgh.
Lancet (1948): i, 857.
 — (1949): ii, 18.
 Medical Research Council (1949): "Vitamin A Requirements of Human Adults", *Spec. Rep. Ser. No. 264*. London.
 Meiklejohn, A. P. (1940): *New Engl. J. Med.*, 223, 265.
Nutrition Reviews (1949a): 7, 220.
 — (1949b): 7, 136.
 Patek, A. J., Post, J., Ratnoff, O. D., Mankin, H., and Hillman, R. W. (1948): *J. Amer. med. Ass.*, 138, 543.
 Pines, K. L., and Perera, G. A. (1949): *Med. Clin. N. Amer.*, 33, 713.
 Rose, W. C., Haines, W. J., Johnson, J. E., and Warner, D. T. (1943): *J. biol. Chem.*, 148, 457.
 Sengupta, S. R., and Howie, J. W. (1949): *Brit. J. Nutrit.*, 2, 313.
 Sinclair, H. M. (1949): *The Practitioner*, 162, 235.
 Smith, D. A. (1946): *Proc. Nutrit. Soc.*, 5, 95.
 Thomson, A. M. (1948): *The Practitioner*, 160, 28.
 Vaughan, J., Dent, C., and Pitt-Rivers, R. (1945): *Proc. Roy. Soc. Med.*, 38, 395.

subdue some public expressions of any personal feeling of deficiency. It now seems reasonably certain that this animal protein factor is, in fact, nothing less than vitamin B₁₂ (*Nutrition Reviews*, 1949b), the anti-pernicious anaemia principle that has been finally isolated from liver almost simultaneously on both sides of the Atlantic.

Protein deficiency and its treatment.—It has already been pointed out (p. 355) that simple calorie deficiency may result in dependent oedema, without any appreciable fall in plasma proteins. It is becoming increasingly clear that "famine" ("war" or "hunger") oedema is not necessarily always due to protein deficiency only, although when protein deficiency coexists with starvation, the resulting reduction in the albumin content of the plasma, and hence of its osmotic pressure, doubtless contributes to the production of oedema (Beattie, Herbert and Bell, 1948).

Protein hydrolysates.—Preparations of *hydrolysed casein* have enjoyed a recent vogue for the treatment of patients suffering from protein deficiency. A recent appraisal (Cuthbertson, 1948) of the value of such preparations supports previous opinions (Vaughan, Deut and Pitt-Rivers, 1945; Davidson and Anderson, 1947; Meiklejohn, unpublished observations). Protein hydrolysate for oral use has little value because, if the patient can take food by mouth, skimmed milk is usually just as nutritious and better tolerated. If, for various reasons, parenteral feeding is obligatory, protein hydrolysate can be given intravenously (Anderson, 1946; Beattie, 1949). But its disadvantages are the large volume of fluid that has to be given, the time taken to give it, the danger of venous thrombosis, and the nausea and vomiting that may follow. For most purposes, intravenous plasma or serum is safer and probably equally effective (Isbister, 1948).

THE VITAMINS

The results of two important studies of experimentally induced vitamin deficiencies in human subjects, carried out under the auspices of the Medical Research Council, have been published in the past year. The first (*Lancet*, 1948) deals with *vitamin C* and the second (Medical Research Council, 1949) with *vitamin A* deficiency. The most interesting results cannot be reviewed here. It is worth noting, however, that one conclusion from these detailed studies is that the daily requirement of these two vitamins "to cover individual variations and to leave a margin of safety", is almost certainly substantially less than previous "recommended allowances". The daily allowances suggested are 30 mg. of ascorbic acid and 2,500 I.U. of Vitamin A.

Vitamin B₁.—In a recent article in *The Practitioner* (Sinclair, 1949) the statement was made that "deficiency of thiamine causes sensorimotor peripheral neuritis". I regretfully disagree with this statement, for reasons explained in detail some time ago (Meiklejohn, 1940), and which still seem

ASBESTOSIS AND CANCER OF THE LUNG

The Factory Department of the Ministry of Labour and National Service has maintained careful observation on the incidence of asbestosis since the disease was first reported upon some twenty-three years ago. Dr. E. R. A. Merewether, H.M. Senior Medical Inspector of Factories, whose original investigations into the disease are well known, has reviewed the 235 deaths that have occurred since between 1942 and 1946, in all of which death has been proved to be due to asbestosis at autopsy. In these 235 deaths, cancer of the lung or pleura was found to be present, either as a cause of death or as a concomitant, in 31 cases, that is, 13.2 per cent., the highest incidence being between the ages of forty-five and sixty-four. Comparison is made between asbestosis and cancer of the lung and silicosis and cancer of the lung. An analysis of 6,884 deaths due to silicosis showed that the incidence of carcinoma of the lung or pleura discovered at post mortem was only 1.32 per cent.; in other words, the incidence of cancer of the lung or pleura is ten times greater with asbestosis.

BERYLLIUM

Since the original publication of a paper on pneumonitis due to beryllium by Van Ordstrand *et al.* in 1943, an extensive literature has grown dealing with the effects of this metal, its salts and compounds, upon the human body. In the main, the pathological effects noticed in man have been due either to the metallic oxide produced in the refining of the metal, or in the preparation and use of those compounds used in fluorescent tubes which go under the generic name of phosphors. Recently Aub and Grier (1949) in America, and Royston (1949) in Great Britain have described cases of acute pneumonitis. In addition to pneumonitis, however, the phosphors, and presumably other compounds of beryllium, may cause a granulomatous condition of the lungs, a condition which tends to progress to a fatal ending. The lungs are not, however, the only organs which may be affected, for Nash, Grier and Freeman (International Congress of Industrial Medicine, 1948) have described cases of subcutaneous granulomas of the skin in people who have cut themselves with broken fluorescent tubes in which the lining was a beryllium-containing phosphor. Much research is being done upon this metal and its compounds, and their pathological effects.

CHEMICAL CARCINOGENESIS

From the time of Percival Potts' first description of cancer of the scrotum in chimney sweeps and his association of the disease with soot, there has been a continued interest in the problem of industrial cancers and their etiology. The most valuable symposium on the subject is, without doubt, in *The British Medical Bulletin*, Vol. 3, Nos. 5 and 6, 1947, in which twenty well-known authorities on the subject have contributed highly specialized,

ADVANCES IN INDUSTRIAL MEDICINE

By ARTHUR J. AMOR, M.D., M.Sc., D.I.H.

Principal Medical Officer, Imperial Chemical Industries, Limited.

THE Ministry of National Insurance is now responsible for the scheduling of industrial diseases—now known as prescribed diseases—of which there are thirty-six, excluding pneumoconiosis and byssinosis. This reduction in the number of what were known as scheduled industrial diseases is due to a re-classification and re-grouping.

The Annual Report of the Chief Inspector of Factories 1947, Cmd. 7621, contains an interesting review of industrial diseases for the period 1939 to 1947. This period covers the war years when the major industrial developments, particularly in terms of the manufacture of explosives, led to added risks and to a much enlarged industrial population. Women formed a large percentage of this industrial population and it is interesting to study the incidence of diseases, particularly until 1942 when, in the main, the peak of the rise was reached. After this there was a great decline in incidence, and it is reasonable to assume that the extension of medical and nursing services, together with improvements and training in welfare work, was responsible for this improvement.

PNEUMOCONIOSIS

Pneumoconiosis still stands out prominently as the most serious of all industrial diseases; the deaths rose from 459 in 1939 to 800 in 1947. Much excellent work upon the elucidation of clinical, radiological and scientific problems relating to the incidence of pneumoconiosis amongst coal miners is being done by the Medical Research team working at Cardiff.

Causal factors.—Whilst it is known that pure silica and asbestos are capable of causing pulmonary fibrosis, doubt has always existed as to the effect of other outside agents in the absence of silica. The literature, however, contains a large number of references to other agents conceivably responsible for producing pulmonary fibrosis, amongst them being cases of fibrosis of the lungs in the silver polisher (Harding, 1948), among diatomaceous earth workers (Vigliani and Mottura, 1948), and changes produced in the lung by the grinding of natural graphite (Harding and Oliver, 1949). Talc has also been reported upon as a dust capable of producing fibrosis of the lungs (McLaughlin *et al.*, 1949). There is an increasing literature on the number of dusts responsible for producing lung changes, but many authors show some hesitation in being dogmatic, and in excluding the possibility that silica had not played some part in the pulmonary change.

ASBESTOSIS AND CANCER OF THE LUNG

The Factory Department of the Ministry of Labour and National Service has maintained careful observation on the incidence of asbestosis since the disease was first reported upon some twenty-three years ago. Dr. E. R. A. Merewether, H.M. Senior Medical Inspector of Factories, whose original investigations into the disease are well known, has reviewed the 235 deaths that have occurred since between 1942 and 1946, in all of which death has been proved to be due to asbestosis at autopsy. In these 235 deaths, cancer of the lung or pleura was found to be present, either as a cause of death or as a concomitant, in 31 cases, that is, 13.2 per cent., the highest incidence being between the ages of forty-five and sixty-four. Comparison is made between asbestosis and cancer of the lung and silicosis and cancer of the lung. An analysis of 6,884 deaths due to silicosis showed that the incidence of carcinoma of the lung or pleura discovered at post mortem was only 1.32 per cent.; in other words, the incidence of cancer of the lung or pleura is ten times greater with asbestosis.

BERYLLIUM

Since the original publication of a paper on pneumonitis due to beryllium by Van Ordstrand *et al.* in 1943, an extensive literature has grown dealing with the effects of this metal, its salts and compounds, upon the human body. In the main, the pathological effects noticed in man have been due either to the metallic oxide produced in the refining of the metal, or in the preparation and use of those compounds used in fluorescent tubes which go under the generic name of phosphors. Recently Aub and Grier (1949) in America, and Royston (1949) in Great Britain have described cases of acute pneumonitis. In addition to pneumonitis, however, the phosphors, and presumably other compounds of beryllium, may cause a granulomatous condition of the lungs, a condition which tends to progress to a fatal ending. The lungs are not, however, the only organs which may be affected, for Nash, Grier and Freeman (International Congress of Industrial Medicine, 1948) have described cases of subcutaneous granulomas of the skin in people who have cut themselves with broken fluorescent tubes in which the lining was a beryllium-containing phosphor. Much research is being done upon this metal and its compounds, and their pathological effects.

CHEMICAL CARCINOGENESIS

From the time of Percival Potts' first description of cancer of the scrotum in chimney sweeps and his association of the disease with soot, there has been a continued interest in the problem of industrial cancers and their etiology. The most valuable symposium on the subject is, without doubt, in *The British Medical Bulletin*, Vol. 3, Nos. 5 and 6, 1947, in which twenty well-known authorities on the subject have contributed highly specialized,

informative and well-documented articles on this subject. A further review of the subject has been made by Heiger (1949), who stresses the importance of the application of fluorescence spectroscopy to the study of carcinogenic substances, and pays tribute to this indispensable technique. A still further review of the chemistry of the carcinogens has been made by Salter (1948), whose conclusions are as follows:—

"Despite a wealth of data indicating carcinogenesis in man from crude mixtures, only three unadulterated agents have thus far been proved carcinogenic for man. These are (1) radiation, (2) betanaphthylamine and (3) arsenic. Chemical compounds which are outstanding carcinogens in rodents have usually proved ineffective in other species and have not been shown effective in man. Therefore carcinogenic activity in rodents should not be used as a criterion of possible danger to man; nor should its absence in rodents be regarded as valid evidence of safety for human workers. At present, the only valid type of evidence of danger of carcinogenesis in man is carefully analysed epidemiological data. As a safety precaution in exposed workers, sensitive microchemical tests should be developed for each individual hazard to prevent more than minimal assimilation of possibly carcinogenic materials".

English authors will agree with what Salter contends are proved carcinogens, particularly after a study of Goldblatt's (1949) excellent article on the vesical tumours induced by chemical compounds.

DUST

The problem of the "all-pervading dusts" is one of the greatest which confronts all who are engaged in preventing disease in industry. In comparison with the handling of dusty materials, the handling of toxic gases and liquids is comparatively easy. Apart from the influence of organic and inorganic dusts upon the health of the workers, there is the problem of bacterial infection and the spread of disease. The Medical Research Council Special Report Series, 1948, No. 262, sets out in some 350 pages the excellent work done by Bourdillon on the study of air hygiene. Bourdillon's general conclusions are interesting, and his comment on the present poor standard of air hygiene is only too true. He discusses the experimental evidence relating to dose of air-borne influenza virus and the severity of the infection, and if the data given were true for human beings then there is considerable evidence for making far greater efforts to improve air hygiene in all places where people work and live. He discusses the chemical and physical means of air sterilization and the difficulties in obtaining conducted in the use of chemical substances in the air, the instability of certain of the dusts used, and the small ratio between killing concentrations and those which produce pathological changes in humans.

The importance to the industrial medical officer is the nature of the dusts. The conference on "Dust in Industry", arranged by the many authors shown in the preceding pages, and held in Leeds University in September 1949, has published by the Society form a most valuable symposium

and perhaps one of the best written in the English language. They are divided into four sections dealing with plant design, the practical aspects of dust problem, fire and explosives hazards, and the last, and perhaps the most interesting, deals with health hazards. The hazards considered are tetraethyl lead dermatitis, silicosis, manganese pneumonitis, arsenic, and a positive method for the determination of free silica in dusts, a problem which has long been a difficult one for industrial medical officers and chemists.

LEGISLATION

The *Factories Act* of 1937 made provision for the medical examination of young persons entering industry but, with certain exceptions, made no provision for their medical supervision once they had entered the industry. This defect in the provision of medical care for young persons in industry has been corrected by the *Factories Act* of 1948, an Act which amends the main Act of 1937 in so far as medical certification for employment now applies, not only to young persons under the age of sixteen, but also to those who have attained the age of sixteen. The medical supervision of young persons is carried out by the Appointed Factory Doctor, who records on an approved medical card the condition of the young person. This is a welcome extension of medical supervision in factories and is comparable with similar developments which have taken place in France and in Belgium. It may probably be regarded as the first step in the introduction of medical supervision in factories on a national scale.

In addition to the care of young persons, the 1948 Act confers additional powers upon the Minister to make special regulations for the medical supervision of persons employed in the factory where there is a risk of injury to health from any substance or material brought into the factory, or from a change in the conditions of work or other conditions in the factory.

A further Section relates to the provision of adequate seating facilities for female workers whose work is normally done standing. This Section of the Act contains certain provisos, and one of the important problems confronting the industrial medical officer and the welfare officer is the type of seat to be provided, not only for those who are able to do their work sitting, but also for those who are only able to take short periods of rest. There is room for much useful research into this problem of seating. During the war several Universities interested themselves in this problem, and the need for careful anatomical studies is no less now than it was in time of war.

In addition to the *Factories Act* of 1948, the *National Insurance Scheme* of the Ministry of National Insurance came into full operation on July 5, 1948. The important part of the Act relating to industry deals with the industrial injury benefits, and there can be no doubt that the new methods of assessment and payment will do much to remove the suspicion which has for a long period surrounded the industrial medical officer when confronted with problems of workmen's compensation. Those who have been

connected with industry will subscribe to the statement that the Act has worked extremely well and has been operated with great humanity.

The Gowers Report.—Apart altogether from legislation, the Report of the Gowers Committee on Health, Welfare and Safety in Non-Industrial Employment is of considerable importance, for it considers the effect of work and working environment on those who are engaged in shops and offices. A large number of statutes, legal acts and bye-laws and regulations controls to some extent the health, the amenities and the environment of people in shops and offices. The Gowers Committee considered these in detail and made recommendations relating to the provision of sanitary accommodation, of heating, lighting and ventilation and the cubic space required per worker, and dealt with that large number of facets of working life which we know under the term "welfare". The Report also deals with the problem of employment in hotels and restaurants, on railways and road transport, agriculture, and a number of miscellaneous occupations. It pays considerable attention to the health and welfare of juveniles and the lifting of excessive weights.

SAFETY IN CHEMICAL WORKS

The problems of safety, general welfare, and nutrition, cannot be separated from those of industrial medicine, and although many large organizations have a safety officer as part of their general management, it is still right that the industrial medical officer should be interested and keenly alive to the problems of safety in factories. The Association of British Chemical Manufacturers has published the third edition of its "Safety Rules" for use in chemical works. Whilst it is true that many of these rules have statutory force by virtue of the Factories Act of 1937 and the relative Regulations, the book is such that it covers in a very short space, and very clearly, the main and important points relating to safety in chemical works, and as a practical handbook should be in the library of every industrial medical officer who deals with the problems relating to chemicals.

References

- Aub, J. C., and Grier, R. S. (1949): *J. industr. Hyg.*, 31, 123.
 Goldblatt, M. W. (1949): *Brit. J. industr. Med.*, 6, 65.
 Harding, H. E. (1948): *Ibid.*, 5, 70.
 —, and Oliver, G. B. (1949): *Ibid.*, 6, 91.
 Heiger, I. (1949): *Ibid.*, 6, 1.
 McLaughlin, A. J. G., Rogers, E., and Dunham, K. C. (1949): *Ibid.*, 6, 184.
 Royston, G. R. (1949): *Brit. med. J.*, 1, 1030.
 Salter, W. T. (1948): *Occupat. Med.*, 5, 441.
 Van Ordstrand *et al.* (1943): *Cleveland Quart.*, 10, 10.
 Vigliani, E. C., and Mottura G. (1948): *Brit. J. industr. Med.*, 5, 148.

CURRENT THERAPEUTICS

XXII.—PITUITARY ADRENAL FUNCTION AND RHEUMATIC DISEASE*

By GEORGE W. THORN, M.D.

Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; Physician in Chief, Peter Bent Brigham Hospital; Consultant in Medical Research, Robert Breck Brigham Hospital

AND THEODORE B. BAYLES, M.D.

Clinical Associate in Medicine, Harvard Medical School; Visiting Physician, Robert Breck Brigham Hospital; Associate in Medicine, Peter Bent Brigham Hospital.

THE MECHANISM OF ADRENAL CORTICAL ACTIVITY

THE adrenal cortical hormones exert a marked influence on a wide variety of metabolic processes in man. The over-all effects exerted by these hormones may be divided into three general groups: (1) electrolyte-regulating effect; (2) regulation of the rate of utilization of carbohydrate, protein and fat; and (3) androgenic and anabolic effect.

Electrolyte-regulating effect of adrenal cortical steroids.—This is characterized by retention of sodium and chloride, increased excretion of potassium, increased plasma and extracellular fluid volume (Kendall, 1948). It has also been shown that desoxycorticosterone-like steroids decrease the concentration of sodium and chloride in sweat (Conn, 1948). The most potent electrolyte-regulating adrenal steroid is 11-desoxycorticosterone, which has been synthesized. The 11, 17-oxysteroids (compounds E and F) exert a relatively weak sodium-retaining effect (Thorn and Forsham, 1949) (figure 1).

Unfortunately, there is no direct measurement of circulating 11-desoxycorticosterone-like factor. Therefore the activity of this steroid must be estimated indirectly, by changes in the renal excretion of sodium, chloride and potassium, by alteration in the mineral composition of thermal sweat and by changes in hæmatocrit and body weight.

The regulation of intermediary metabolism by 11- and 11, 17-oxysteroids.—The second group of metabolic activities modified by the adrenal cortex involves the regulation of carbohydrate, protein and fat utilization, control of lymphoid tissue and circulating eosinophils. The effects of this type of compound are characterized by:—

(1) An increase in blood glucose level and liver glycogen stores.

(2) An increased conversion of protein to carbohydrate (increased gluconeogenesis). Recent studies indicate that this effect is accomplished,

* From the Department of Medicine, Harvard Medical School, Boston, Mass.

connected with industry will subscribe to the statement that the Act has worked extremely well and has been operated with great humanity.

The Gowers Report.—Apart altogether from legislation, the Report of the Gowers Committee on Health, Welfare and Safety in Non-Industrial Employment is of considerable importance, for it considers the effect of work and working environment on those who are engaged in shops and offices. A large number of statutes, legal acts and bye-laws and regulations controls to some extent the health, the amenities and the environment of people in shops and offices. The Gowers Committee considered these in detail and made recommendations relating to the provision of sanitary accommodation, of heating, lighting and ventilation and the cubic space required per worker, and dealt with that large number of facets of working life which we know under the term "welfare". The Report also deals with the problem of employment in hotels and restaurants, on railways and road transport, agriculture, and a number of miscellaneous occupations. It pays considerable attention to the health and welfare of juveniles and the lifting of excessive weights.

SAFETY IN CHEMICAL WORKS

The problems of safety, general welfare, and nutrition, cannot be separated from those of industrial medicine, and although many large organizations have a safety officer as part of their general management, it is still right that the industrial medical officer should be interested and keenly alive to the problems of safety in factories. The Association of British Chemical Manufacturers has published the third edition of its "Safety Rules" for use in chemical works. Whilst it is true that many of these rules have statutory force by virtue of the Factories Act of 1937 and the relative Regulations, the book is such that it covers in a very short space, and very clearly, the main and important points relating to safety in chemical works, and as a practical handbook should be in the library of every industrial medical officer who deals with the problems relating to chemicals.

References

- Aub, J. C., and Grier, R. S. (1949): *J. industr. Hyg.*, 31, 123.
 Goldblatt, M. W. (1949): *Brit. J. industr. Med.*, 6, 65.
 Harding, H. E. (1948): *Ibid.*, 5, 70.
 —, and Oliver, G. B. (1949): *Ibid.*, 6, 91.
 Heiger, I. (1949): *Ibid.*, 6, 1.
 McLaughlin, A. J. G., Rogers, E., and Dunham, K. C. (1949): *Ibid.*, 6, 184.
 Royston, G. R. (1949): *Brit. med. J.*, i, 1030.
 Salter, W. T. (1948): *Occupat. Med.*, 5, 441.
 Van Ordstrand *et al.* (1943): *Cleveland Quart.*, 10, 10.
 Vigliani, E. C., and Mottura G. (1948): *Brit. J. industr. Med.*, 5, 148.

if adequate quantities of either of these hormones are administered. It appears that compounds E and F may compete with 11-desoxycorticosterone in its action on electrolyte regulation. Thus, in the presence of excess sodium retention induced by desoxycorticosterone acetate, treatment with large doses of compound E may result, not in further sodium retention, but in increased sodium excretion.

An approximate measure of the amount of "carbohydrate-regulating" factors secreted may be achieved by following the urinary excretion of 11-oxysteroids or "cortin-like" substances (Talbot *et al.*, 1947), or, more simply, by noting a fall in the level of the circulating eosinophils, or by observing the rise in the urinary uric acid-creatinine ratio which follows an increased blood level of 11- and 11,17-oxysteroids (Thorn and Forsham, 1949). Recent evidence suggests that the adrenal cortex secretes predominantly compound F (Haines *et al.*, 1949).

The androgenic and anabolic effect of adrenal androgens.—The third group of adrenal steroids are those referred to as the adrenal androgens. It is assumed that these substances exert an effect similar to that of the testicular androgens, which consists of masculinization, with retention of nitrogen, phosphorus, potassium, sodium and chloride (Albright, 1942-43). This effect has been characterized as the androgenic or anabolic hormone effect. In the female it is evident that nearly all androgenic effect is derived from the adrenal cortical androgens, whereas in the male, the adrenal androgens appear to account for only two-thirds of the androgenic substances, the remainder being derived from the testes. Adrenal androgens are related in structure to testosterone, but carry an oxygen group in position 11 (adrenosterone). The secretion of androgenic substances or the administration of these steroids is evidenced by a rise in urinary 17-ketosteroids, their excretory product.

PRACTICAL CONSIDERATIONS IN ADRENAL HORMONE THERAPY

Two groups of adrenal cortical hormone preparations are available commercially at the present time: whole adrenal cortical extracts derived from beef or hog adrenals, and synthetic desoxycorticosterone acetate.

In the case of *adrenal insufficiency*, the salt-retaining factors are easily substituted for by the administration of synthetic desoxycorticosterone acetate (DCA) in the form of a solution in oil (5 mg. per ml.), a macro-suspension in various solvents, or in the form of subcutaneously implanted tablets or pellets weighing 125 mg. or 75 mg. each. Such pellets give off 0.5 and 0.3 mg. respectively of DCA daily. These substances are ineffective in the therapy of rheumatic diseases.

Substitution therapy with "carbohydrate-regulating" factors has been possible in primary adrenal insufficiency by the administration of whole extracts of cattle or hog adrenal. Such commercial extracts contain relatively small quantities of the known steroid hormones. Aqueous whole adrenal

not by an increased catabolism of body protein, but rather by diverting amino-acid radicals to pyruvic acid and glucose (anti-anabolic effect).

(3) An increased mobilization of depot fat and its enhanced utilization, thus sparing carbohydrate. An increased intestinal absorption of fat has been observed following the administration of this group of steroids and, although relatively unimportant calorically, it is of theoretical interest.

(4) An increase in the renal clearance of uric acid, resulting in the excretion of large quantities of urate, both in normal subjects and in patients with gout.

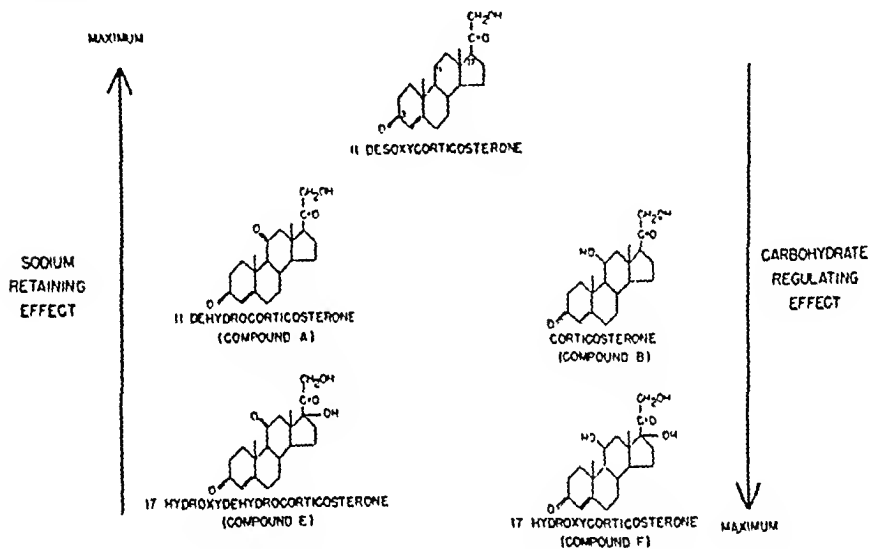


FIG. 1.—The relation of chemical structure to sodium-retaining and carbohydrate-regulating effect.

(5) A lysis of fixed lymphoid tissue and a transitory decrease in circulating lymphocytes. A somewhat more permanent effect is observed in the case of the circulating eosinophils, which almost completely disappear from the blood during the period of action of the hormone.

Examples of the "carbohydrate-regulating" adrenal cortical steroids are the 11-oxysteroids, Kendall's compounds A (11-dehydrocorticosterone) (Forsham *et al.*, 1948a) and B (corticosterone), and the much more active 11,17-oxysteroids, Kendall's compounds E (17-hydroxy-11-dehydrocorticosterone) (Thorn *et al.*, 1949) and F (17-hydroxycorticosterone) (figure 1). The effects on lymphoid tissue and eosinophils are exerted only by the 11,17-oxysteroids. In all but electrolyte effects, these latter substances are superior to the 11-oxysteroids and to 11-desoxycorticosterone. Although the salt-retaining effect of the 11,17-oxysteroids is approximately 1/30 that of 11-desoxycorticosterone, adequate salt retention may be obtained by the use of relatively large quantities of these substances. It is therefore possible in the case of compounds E and F to maintain a satisfactory electrolyte balance

of the above effects when given ACTH. Furthermore, the studies on patients with Addison's disease prove that the changes following ACTH are due to the secondary outpouring of the adrenal cortical steroids, rather than to a primary effect of ACTH itself. It is therefore obvious that the administration of ACTH would not be a suitable means for increasing adrenal hormone secretion in patients with adrenal cortical insufficiency due to primary disease of the adrenal or to physiological exhaustion.

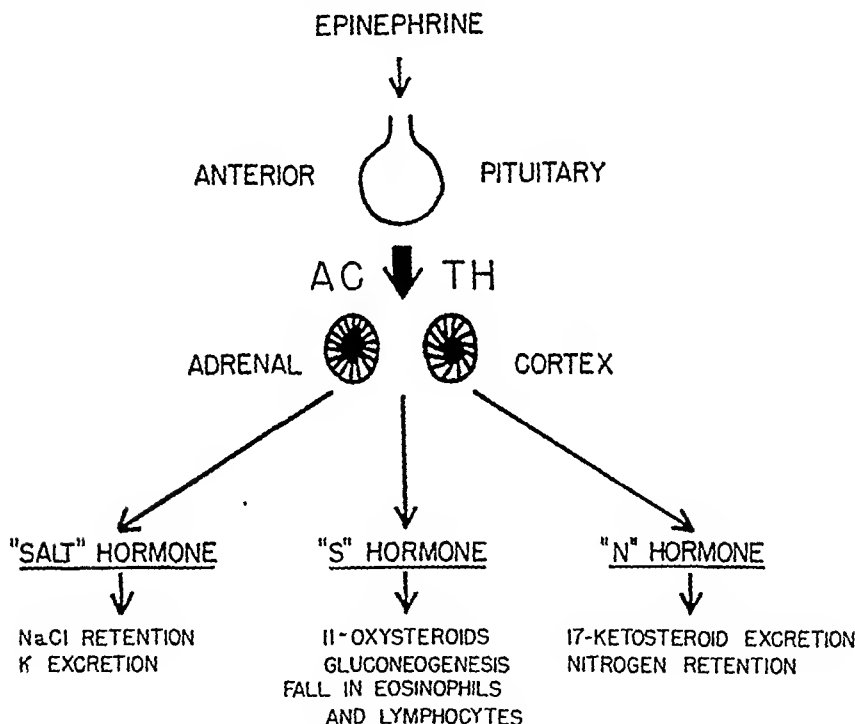


FIG. 2 —Schema of pituitary adrenal axis. ACTH stimulating adrenal cortex to produce active steroid hormones

Epinephrine stimulation of the anterior pituitary-adrenal cortical system.— On the basis of earlier animal experiments by Long and others (Long, 1947; Vogt, 1945), in which it was shown that epinephrine was capable of stimulating an intact pituitary-adrenal cortical system, studies in men were carried out (Recant *et al.*, 1949).

It was observed that a single injection of 0.3 mg. of epinephrine subcutaneously in a patient with an intact pituitary and adrenal cortex, was followed by a fall in the level of circulating eosinophils, most marked after four hours. In normal individuals, this amounted to 50 per cent or more; in patients with pituitary deficiency, or in patients with Addison's disease, a small or negligible fall was observed with this dose of epinephrine. Larger doses of epinephrine (1 mg. or more) appear to be capable of activating adrenal cortical remnants in patients with advanced Addison's disease, but not in patients with severe pituitary ACTH deficiency. Repeated in-

extracts are less potent than "lipo-adrenal cortex" (Upjohn), a concentrate of hog adrenal in oil, each millilitre of which is equivalent to 2 mg. of compound E acetate. In the treatment of diseases such as *rheumatoid arthritis*, obviously very large quantities of whole adrenal extract will be required to induce an effect comparable to that obtained from 50 to 100 mg. of compound E daily. By 1950 limited amounts of compound E acetate should be available as a super-saturated solution in oil, containing 10 mg./ml. Compound F, which has not been synthesized, is derived from hog adrenals. Doses of the same order of magnitude as compound E will probably be required in the treatment of rheumatoid arthritis. However, because of the greater solubility of compound F, it will be necessary to increase the frequency of administration, as compared with compound E acetate.

PITUITARY ADRENOCORTICOTROPHIC HORMONE (ACTH)

Since purified pituitary adrenocorticotrophic hormone has become available in quantities adequate for clinical investigation, it has been possible to study the effect of administering this trophic substance on the secretion of adrenal steroids in man (Forsham *et al.*, 1948b; Mason *et al.*, 1948). Four hours after the injection of a single dose of 25 mg. of purified ACTH (Armour Standard*) there is a profound fall in circulating eosinophils and a rise in urinary uric acid excretion (increased uric acid-creatinine ratio). Repeated administration of ACTH, in doses of 10 mg., injected intramuscularly every six hours, 40 mg. daily (Armour Standard) has resulted in marked sodium and chloride retention, with initial potassium loss; a rise in urinary 11-oxysteroid excretion and in the level of circulating 11-oxysteroids as determined by biological assay (Halberg); a rise in blood sugar level; a fall in circulating eosinophils; a rise in uric acid excretion; and an increase in urinary 17-ketosteroid excretion to the upper limit of normal. Prolonged administration of the preparation gives rise to a chemical pattern and a clinical picture suggestive of mild Cushing's syndrome. Thus, in man, it appears that with an adrenal capable of responding, stimulation of the gland by ACTH is followed by an increased secretion of adrenal steroids, which gives rise to all the known effects previously observed with crystalline adrenal steroid preparations (fig. 2). The fall in circulating eosinophils affords the most sensitive indicator of adrenal cortical activation and may change before any of the other signs of adrenal cortical activation have become manifest. In addition to increasing the adrenal hormone level in patients with intact adrenals, ACTH stimulation has served a very useful purpose in providing a clear-cut test for adrenal cortical insufficiency (Thorn *et al.*, 1948). Thus, patients with Addison's disease fail to show any

* The ACTH used in these studies was supplied by Dr. John R. Mote of the Armour Laboratories, Chicago 9, Illinois. The Armour Standard is of such potency that 4 gammas given intramuscularly to a hypophysectomized rat will lead to a fall in adrenal ascorbic acid of from 20 to 40 per cent.

lates ACTH secretion. Through this neuro-humoral system, the adrenal cortex may be activated to secrete 11,17-oxysteroids by a number of non-specific stresses and emotional factors (fig. 3).

Depression of circulating eosinophils has been demonstrated in a variety of modern stresses, but the extent to which adrenal cortical activation may be accomplished by such non-specific means awaits further investigation. It would appear that the stimulatory effect upon the central nervous system of such noxious stimuli is the basis of pituitary ACTH activation. Adrenal cortical reserve was measured by means of four-hour and forty-eight-hour ACTH tests and/or four-hour epinephrine tests in 21 patients with rheumatoid arthritis (Thorn and Forsham, 1949). The four-hour ACTH test, using the intramuscular injection of 25 mg. of ACTH, and its effect on the circulating eosinophils four hours later (Thorn, *et al.*, 1948) was carried out in 10 patients, nine of whom showed a normal or low normal response. The one patient who did not respond subsequently proved to be refractory also to therapy with ACTH. This essentially normal response in all but one of this group suggests that the available reserve of this adrenal cortex was not noticeably impaired by the rheumatic state. This concept is confirmed by the results of the forty-eight-hour tests, which in most instances were a continuation of the four-hour tests and were carried out using 10 mg. of ACTH every six hours. All of the known functions of the adrenal cortex were stimulated in all but one of the patients. Starting on July 23, 1948, the epinephrine test, which consists of giving 0.3 mg. of epinephrine subcutaneously and of calculating the fall of eosinophils at the end of four hours, was carried out on 14 patients with rheumatoid arthritis. The average fall in these patients of 50 per cent. was slightly less than in a similar group of normal subjects who showed a mean 64 per cent. fall. However, the spread of the results in the tests on patients with rheumatoid arthritis was considerably greater than in the normal control group. Several of the patients who failed to respond normally to epinephrine responded well to ACTH. Such a dissociation may be fortuitous or else may suggest a possible deficiency in the hypothalamic-pituitary link in adrenal cortical activation (fig. 3).

THE EFFECT OF ACTH THERAPY ON RHEUMATOID ARTHRITIS

With the discovery by Hench, Kendall, Slocumb and Polley (1949) that compound E, given in large doses (100 mg. per day), is effective in the treatment of rheumatoid arthritis, studies were made on the effect of the prolonged administration of ACTH to patients with rheumatoid arthritis.

Ten patients were treated for from two to thirty days with 40 mg. of ACTH per day, given in divided doses of 10 mg. every six hours. Of the patients treated, 5 were males and 5 females, varying in age from twenty-five to sixty-one years. The arthritis was severe or moderately severe in nine cases and mild in one case; and the duration of the disease varied from three months to twenty-eight years. In every instance, in which the adrenal cortex responded, improvement occurred,

jection of small quantities of epinephrine (0.5 to 0.8 mg.), every six hours over a period of weeks, has resulted in a continued stimulation of adrenal cortical steroid hormone production, as evidenced by eosinopenia, moderately increased urinary 11-oxysteroid excretion, and a doubling of the urinary 17-ketosteroid excretion. It is also evident that the four-hour epinephrine test is a useful screening technique for detecting both anterior pituitary ACTH or adrenal cortical insufficiency (fig. 3).

In contrast to the uninhibited stimulation of adrenal cortical hormones which follows the repeated administration of ACTH, epinephrine administration has the disadvantage of losing much of its effectiveness as an adrenal cortical stimulator, since endogenous ACTH production is inhibited by a rising titre of adrenal cortical steroids. This inherent disadvantage will be found with any substance which stimulates pituitary ACTH production.

STIMULATION OF THE HYPOTHALAMIC PITUITARY-ADRENAL CORTICAL SYSTEM BY STRESS

Anterior hypothalamic centres have recently been shown to form an essential link in the activation of pituitary ACTH secretion following conditions of stress, as well as epinephrine administration (Hume, 1949). Upon nervous stimulation or contact with circulating epinephrine, a humoral substance appears to be secreted by cells of the anterior hypothalamus which stimu-

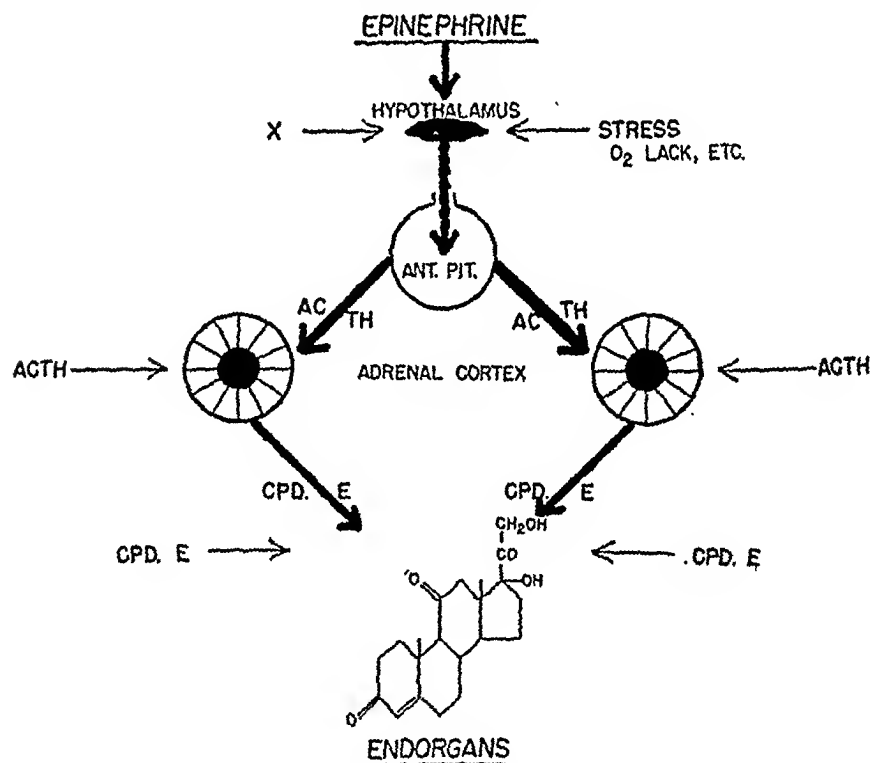


FIG. 3.—Known mechanism of adrenal cortical stimulation.

return of symptoms, including stiffness and pain in the joints, a rise in sedimentation rate and a loss of the euphoria.

Milder cases of rheumatoid arthritis show a somewhat more lasting effect after ACTH therapy, although the majority of cases returned toward, but

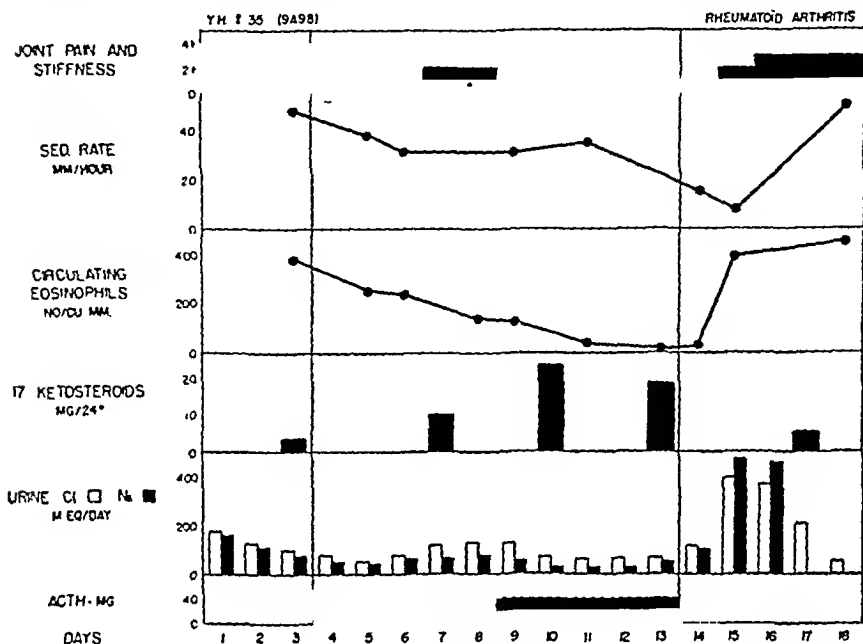


FIG. 5.—Treatment with ACTH.

did not reach, their pre-treatment status. The reversion to pre-treatment status may be minimized, but not eliminated, by withdrawing the adrenal cortical stimulation gradually. Thus, following 10 mg. of ACTH intramuscularly every six hours, this same dose was given every eight hours for a week, then every twelve hours for another week, and then once a day for a short period before being discontinued altogether.

Epinephrine administration.—Because of the limited quantities of synthetic compound E and natural ACTH, attempts were made to increase the degree of pituitary adrenal stimulation by less specific methods. Since epinephrine has been shown to stimulate ACTH production in man, patients with rheumatoid arthritis were given a stimulating dose of epinephrine every six hours throughout the day and night. This therapy in two patients with rheumatoid arthritis resulted in a very slight but definite improvement, although again the maximum improvement observed was far less than that which occurred with ACTH or which might have been expected with 100 mg. of synthetic compound E. Definite adrenal cortical activation occurred, although apparently not sufficient in terms of its beneficial effect on the rheumatoid arthritis state (fig. 6). The use of epinephrine at the

One patient was treated for 30 days, two patients were treated for two weeks, and 7 for forty-eight hours. Within four to twenty-four hours following the initial administration of ACTH, clinical improvement was observed, in every way similar to that reported by Hench and his group, who used 100 mg. of synthetic compound E daily (Hench *et al.*, 1949).

The most characteristic immediate change was loss of stiffness in the joints. This was followed by improvement in the patient's general sense of well-being, culminating in a euphoric state. With more prolonged administration, there was increased range of motion in the joints and loss of pain. Objective evidence of improvement was found in a progressive fall in the blood sedimentation rate, often reaching normal levels after about one week. Evidence for a generally increased adrenal hormone secretion in those patients given ACTH was provided: (1) by a sustained fall in the level of circulating eosinophils; (2) by a marked rise in 17-ketosteroid excretion; and (3) by sodium retention. Illustrative cases are shown in fig. 4 in their

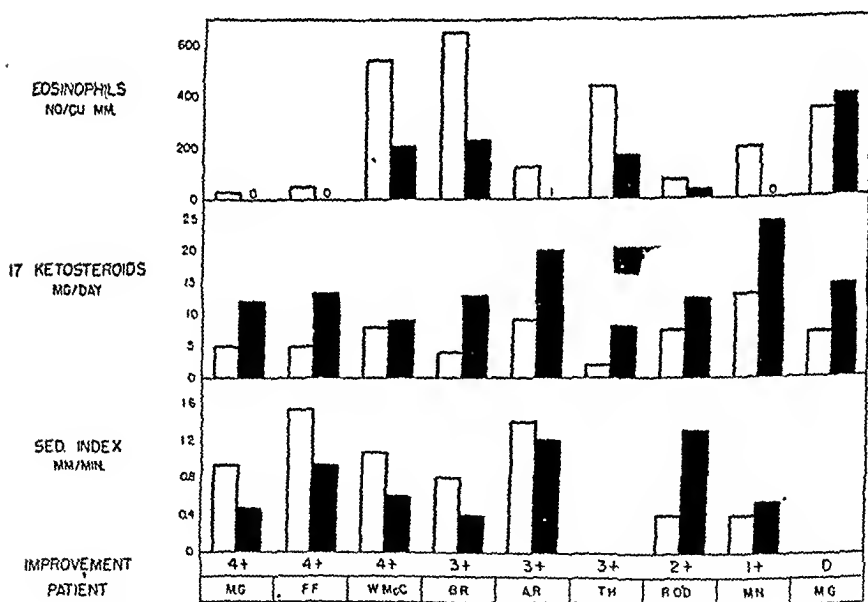


FIG. 4.—Changes following forty-eight hours ACTH in rheumatoid arthritis.

reaction to 48 hours of ACTH (95 mg.). It will be noted that the one patient who failed to show any improvement on forty-eight hours of ACTH did not have an eosinophil fall, although urinary 17-ketosteroids rose. The patient who showed only 1+ improvement was the single case of the group in which the arthritis was initially mild. A typical case on prolonged therapy with ACTH is presented in fig. 5.

Withdrawal of ACTH therapy after two to fourteen days of treatment in 10 patients was followed in twelve to twenty-four hours by a partial

return of symptoms, including stiffness and pain in the joints, a rise in sedimentation rate and a loss of the euphoria.

Milder cases of rheumatoid arthritis show a somewhat more lasting effect after ACTH therapy, although the majority of cases returned toward, but

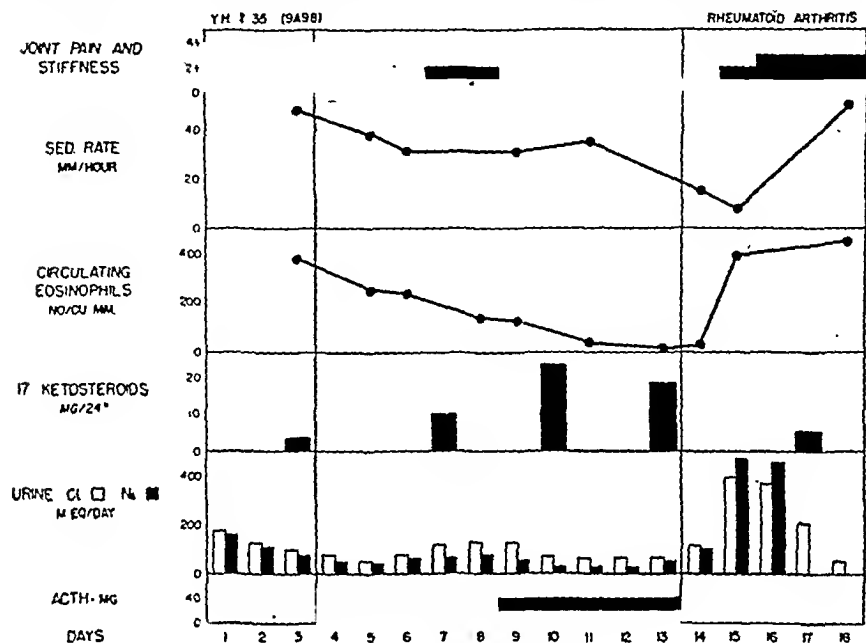


FIG. 5.—Treatment with ACTH.

did not reach, their pre-treatment status. The reversion to pre-treatment status may be minimized, but not eliminated, by withdrawing the adrenal cortical stimulation gradually. Thus, following 10 mg. of ACTH intramuscularly every six hours, this same dose was given every eight hours for a week, then every twelve hours for another week, and then once a day for a short period before being discontinued altogether.

Epinephrine administration.—Because of the limited quantities of synthetic compound E and natural ACTH, attempts were made to increase the degree of pituitary adrenal stimulation by less specific methods. Since epinephrine has been shown to stimulate ACTH production in man, patients with rheumatoid arthritis were given a stimulating dose of epinephrine every six hours throughout the day and night. This therapy in two patients with rheumatoid arthritis resulted in a very slight but definite improvement, although again the maximum improvement observed was far less than that which occurred with ACTH or which might have been expected with 100 mg. of synthetic compound E. Definite adrenal cortical activation occurred, although apparently not sufficient in terms of its beneficial effect on the rheumatoid arthritis state (fig. 6). The use of epinephrine at the

termination of a course of ACTH holds promise as a means of increasing endogenous ACTH production and of buffering the sudden falling off in adrenal cortical activity, which invariably follows the discontinuance of ACTH. A number of methods of non-specifically stimulating the pituitary

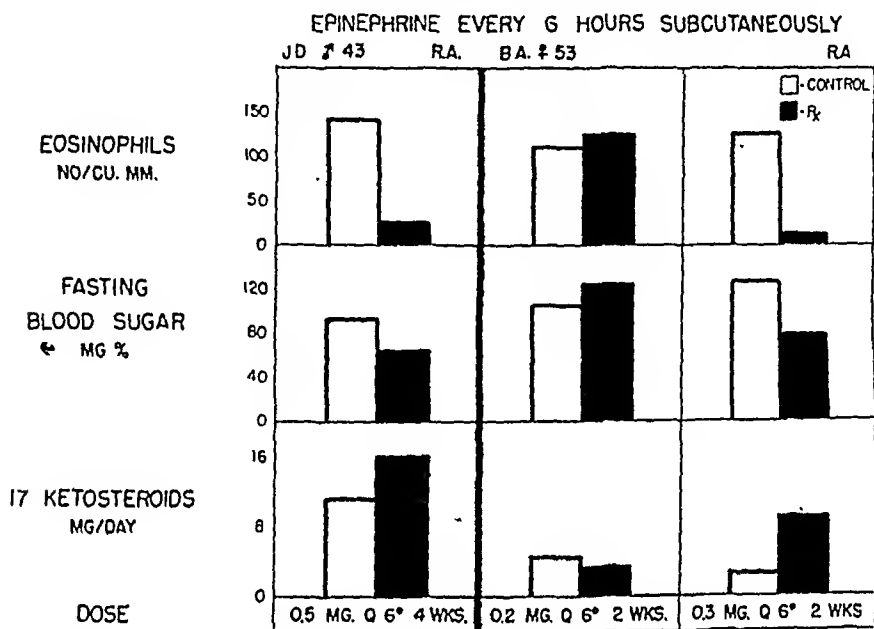


FIG. 6.—The effect of epinephrine on two patients with rheumatoid arthritis. Note the ineffectiveness of a 0.2 mg. dose of epinephrine. Slight clinical effect on the disease process.

to increase its ACTH output, and thereby the adrenal cortical secretion, are now being studied in patients with rheumatoid arthritis.

In addition to the studies carried out with ACTH and epinephrine, an attempt was made to improve the clinical condition of patients with rheumatoid arthritis by the administration of large quantities of *adrenal cortical extract*. Two ml. of lipo-adrenal cortex (Upjohn) were given intramuscularly, every three to four hours, for one to three days, to 5 patients with rheumatoid arthritis. The total daily dose of lipo-adrenal cortex was 12 to 15 ml. This corresponds to approximately 60 to 75 ml. of aqueous whole adrenal extract. Patients with rheumatoid arthritis given this treatment showed very slight improvement, but the magnitude of change was in no way comparable to that observed following ACTH in our group, or following compound E as described by the Mayo Clinic group. This relative ineffectiveness appears, in all probability, to be due to the fact that the total amount of extract administered contained much less than the equivalent of 100 mg. of compound E, or the quantity of compound E or F released by the adrenal cortex upon stimulation by 40 mg. of ACTH, which was given in our studies.

THE EFFECT OF ACTH ADMINISTRATION ON RHEUMATIC FEVER

The response to ACTH of patients with acute rheumatic fever is more striking than that obtained in patients with rheumatoid arthritis, in whom previous joint deformities persist in spite of ACTH-induced improvement. Acute rheumatic fever has been treated for periods varying from eight to fourteen days, with 10 mg. of ACTH given intramuscularly every six hours.

An illustrative case of an eleven-year old girl is shown in figure 7. This patient was given ACTH early in her second known rheumatic attack, which was associated with subcutaneous nodules, arthritis, pericarditis, and myocarditis, as suggested by a protodiastolic gallop and electrocardiographic changes. The patient was taken off acetylsalicylic acid three days before treatment with ACTH was begun.

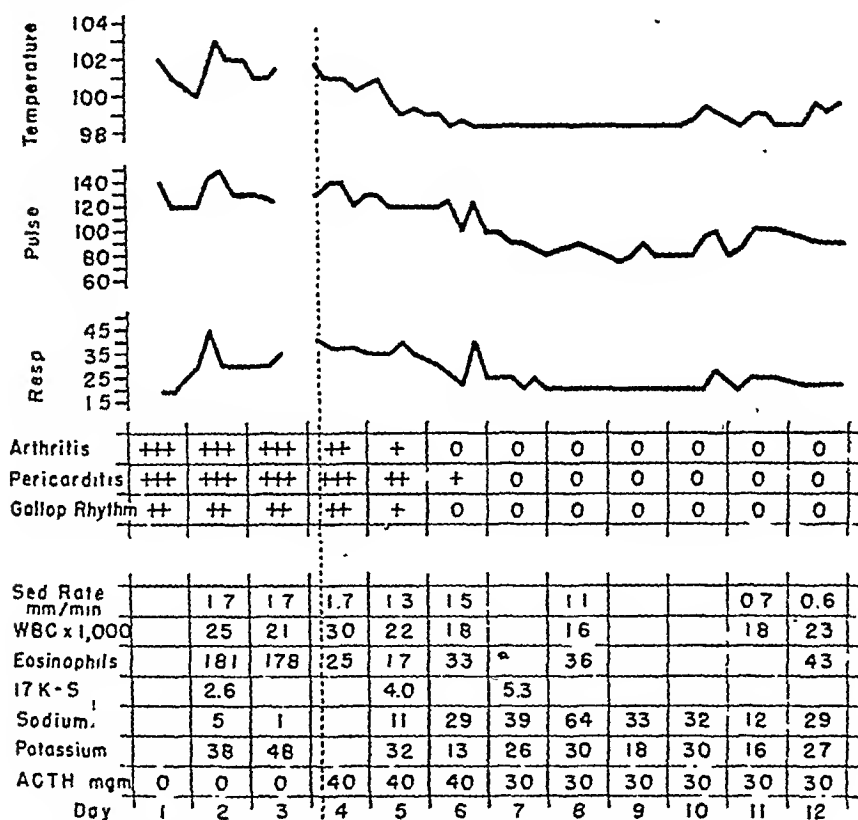


FIG. 7.—Chart of ACTH treatment of an eleven-year old girl with active rheumatic fever. Sodium and potassium values refer to the daily urinary output in milli-equivalents on a constant diet.

It will be noted that all of the known adrenal cortical secretions appeared to be increased by ACTH, although the relative proportion by which the individual factors were augmented cannot be ascertained by current analytical methods. The contamination of Armour ACTH by posterior

pituitary principle and the consequent retention of water leads to a rapid weight gain in most subjects being given ACTH. In a patient with incipient heart failure such a possibility is very undesirable. However, in the limited number of cases treated and with the dose of ACTH employed it was found that the improvement in cardiac efficiency, with its beneficial effect on renal circulation, led to an increased urinary volume, rather than to water retention during a period of one week. The over-all benefits were identical with those obtained with compound E acetate (Hench *et al.*, 1949).

EFFECT OF ACTH ADMINISTRATION ON LUPUS ERYTHEMATOSUS DISSEMINATA

Two patients with acute disseminated lupus erythematosus showed marked clinical improvement with rapid disappearance of the typical butterfly rash when given 10 mg. of ACTH intramuscularly every six hours. A representative case is shown in fig. 8. The low initial eosinophil count in

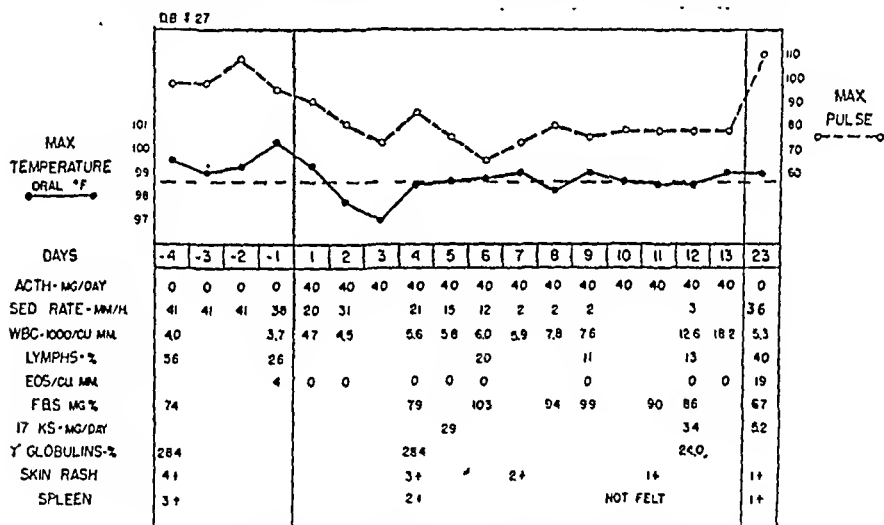


FIG. 8.—Effect of ACTH in a patient with disseminated lupus erythematosus.

this instance was found also in another case and is a consequence of bone marrow hypoplasia with normal adrenal cortical function, rather than a sign of greatly increased adrenal cortical activity as in Cushing's syndrome, in which a marked eosinopenia is diagnostic (Thorn and Forsham, 1949). It should be noted that the gamma globulins, normally 12 to 15 per cent. of the total protein, did not fall below 20 per cent. during the course of ACTH, yet the sedimentation rate was decreased and the patient was clinically improved. It is also of interest that the initial striking clinical improvement was obtained without any change in the circulating gamma globulins. Again, all major adrenal cortical functions appeared activated. Forty mg. of ACTH were given daily for thirteen days, followed by 20 mg.

daily for four days. Five days after discontinuing ACTH therapy, the characteristic leucopenia, elevated sedimentation rate and enlarged, tender spleen returned. In spite of this, the patient was still feeling well and the rash had not reappeared. The treatment had thus led to striking temporary improvement which left the patient in a better clinical state, but did not lead to a cure. The use of such therapy in conjunction with established methods of treatment may prove to be of benefit in the future.

EFFECT OF ACTH ADMINISTRATION ON GOUTY ARTHRITIS

In studying the effect of ACTH on patients with gouty arthritis, it was found that treatment with the hormone caused a large increase in urinary uric acid excretion with a concomitant fall in serum uric acid levels. The clinical improvement was striking and rapid. This improvement was characterized by increased joint mobility, decreased pain and softening of tophi. Whilst the rise in uric acid excretion is no greater than that achieved by the administration of 5 gm. of acetylsalicylic acid per day (Talbot, 1943), the over-all clinical improvement is much more marked with ACTH administration. Upon withdrawal of ACTH, a mild gouty attack occurred after two days. This phenomenon has been reported by Hellman (1949). An illustrative case is shown in fig. 9.

	AL 263									GOUT		
EOSINOPHILS NO/CU MM.	338	339		17		2	8			241	427	
BLOOD SUGAR MG. %	86	74		105		86	89	94		68	59	
SERUM URIC ACID MG. %	9.6	10.5		9.2	6.7	5.8	5.4	5.8		8.6	9.1	
URINARY URIC ACID MG. %	400	403	404	864	1300	1000	1100	1248	1145	500	575	598
17 KETOSTEROIDS MG/DAY		17.4		18.4		29.4						
DAYS ACTH	1	2	3	4	5	6	7	8	9	10	11	12
	0			40 MG/DAY						0		

FIG. 9.—Effect of ACTH on severe gout.

DISCUSSION

Rheumatic fever, disseminated lupus erythematosus, and rheumatoid

arthritis may be viewed as related mesenchymal diseases, characterized by a non-specific inflammatory reaction, presumably brought on by a peculiar susceptibility of the host to certain bacterial or tissue products. Such disease states are apparently favourably altered by a sudden marked increase in the titre of circulating 11,17-oxysteroids or related compounds of adrenal origin. With a sudden increase in the level of these steroids, the progress of the inflammatory reaction, vessels, and synovia is temporarily arrested. The majority of patients with these diseases appear to possess normal adrenal cortical reserve function, but normally do not spontaneously increase the activity of their adrenal cortex so tremendously. Is such an activation an essential part of the normal defence mechanism? If so, is it absent in those afflicted with mesenchymal disease? Or is the massive activation of adrenal cortical hormone production by ACTH merely a therapeutic implement acting pharmacologically and favourably upon the patient's reaction pattern to the disease? Evidence in support of this concept is the fact that 100 mg. of compound E are needed to alter significantly the course of rheumatic disease, whereas patients with complete adrenal insufficiency may be maintained with 10 to 20 mg. of compound E daily. Effective therapy is only attained when the level of hormone is clearly increased, either from subnormal to above normal, or from normal to above normal.

Obviously, ACTH therapy will only be effective in patients in whom a normal adrenal cortical response is obtained. A marked decrease in circulating eosinophils following ACTH therapy is a valuable indication of increased secretion of 11,17-oxysteroids; 11,17-oxysteroids appear specific in their ability to depress circulating eosinophils (Hills *et al.*, 1948) and lyse lymphoid tissue, and to date are the only type of steroid which has been shown to exert a beneficial effect in rheumatic disease (Hench *et al.*, 1949). Since they are synthesized from bile acids, the supply of these steroids will always be limited; therefore a search for 17-oxysteroids derived from cholesterol or plant sterols and their trial in the rheumatic state becomes of great practical importance. ACTH, too, is limited by the number of pituitary glands available at any one time; thus the search for effective non-specific pituitary adrenal stimulants must be continued.

The mode of action of 11,17-oxysteroids in these diseases is unknown. Improvement is observed in most patients within four to five hours. Blood sedimentation rate usually falls within forty-eight hours after treatment is begun, but the maximal change may not occur for ten to fourteen days. The initial changes which occur, such as loss of stiffness and increased capacity to move joints without pain, suggest that there has been a decrease in some "stiffness factor" and an immediate reduction in the chronic inflammatory reaction. Possible causes of these changes would be the effect of the hormone on enzyme systems, antigen-antibody relationships or tissue permeability (Opsahl, 1949). The singular specificity of adrenal

steroids in their effect on rheumatic diseases is suggested by the prompt response to compound E and the ineffectiveness of desoxycorticosterone and dehydrocorticosterone acetate. Excessive DCA treatment in patients with Addison's disease is often associated with increased stiffness of the joints and/or arthralgia, but clinical rheumatoid arthritis is quite uncommon (Thorn *et al.*, 1942). It is of interest that Selye has been able to accumulate a large amount of experimental evidence suggesting that arthritis may be induced in rats by the administration of excessive amounts of desoxycorticosterone (Selye *et al.*, 1944).

The improvement in gout brought on by ACTH is apparently not due to increased renal uric acid clearance alone, but must also involve some direct effect on the joint tissue. Even though the effect of salicylates on the uric acid excretion is greater, the clinical improvement noted is far less than with ACTH.

The dangers of continued ACTH or compound E acetate treatment are principally the undesirable side-effects associated with a long-continued high level of adrenal steroids. In the case of long-continued ACTH administration, the possibility of persistent adrenal hyperplasia must be borne in mind. A Cushing-like syndrome has been reported during the prolonged administration of compound E (Hench *et al.*, 1949). On 40 mg. of ACTH per day this danger is reduced, because although full adrenal cortical activation is achieved there has been a rapid return of function to normal or subnormal levels in all instances studied thus far. On the other hand, the pituitary ACTH mechanism is suppressed by exogenous ACTH whilst the full adrenal cortex is stimulated, whereas with compound E both the adrenal cortex and the anterior pituitary gland may become atrophic. Thus, withdrawal of compound E therapy leads to a more acute, temporary adrenal cortical deficiency than does the withdrawal of ACTH therapy. In order to minimize this sudden reduction in adrenal cortical activity, it would appear desirable to administer ACTH for twenty-four to forty-eight hours following the withdrawal of compound E therapy.

The beneficial effect of 11,17-oxysteroid therapy in the rheumatic diseases marks a great advance in therapeutic research. Adrenal cortical hormone therapy does not, however, appear to alter the fundamental cause of the inflammatory changes which characterize these diseases. The use of adrenal cortical steroids or adrenal cortical stimulants will do much to further fundamental research in the field of rheumatic disease. Their exact value as therapeutic agents remains to be worked out.

SUMMARY

The major metabolic changes induced in man by adrenal cortical steroids have been described. The remarkable observations of Hench, Kendall *et al.* (1949) on the effect of compound E therapy in patients with rheumatoid arthritis have been extended by the use of pituitary adrenocorticotrophic

hormone (ACTH). The status of the adrenal cortical function in 21 patients with rheumatoid arthritis has been ascertained and found to be essentially normal in 18 of the patients. There appears to be a wide variation in the state of adrenal cortical function from patient to patient, without apparent correlation with the severity or manifestations of the disease. In 9 patients with rheumatoid arthritis in whom pituitary adrenocorticotrophic hormone was capable of stimulating the adrenal cortex to increased activity, there was striking clinical improvement and a reversal of abnormal laboratory findings. Three patients with rheumatic fever and two patients with disseminated lupus erythematosus were similarly improved by ACTH therapy, as was one case of gout.

With the present inadequate supply of synthetic compound E acetate and pituitary ACTH, non-specific methods for stimulating an intact pituitary-adrenal system and naturally occurring adrenal cortical extracts have been tried with variable success in the treatment of rheumatic diseases.

Associated in these studies were Dr. Peter H. Forsham and Dr. S. Richardson Hill, Jun., of the Peter Bent Brigham Hospital. Dr. J. Sydney Stillman and Dr. Stephen Smith III, of the Robert Breck Brigham Hospital, and Dr. Joseph E. Warren of The House of The Good Samaritan; all of the Department of Medicine, Harvard Medical School, Boston, Mass.

References

- Albright, F. (1942-43): *Harvey Lect.*, 38, 123.
 Conn, J. W. (1948): *Arch. intern. Med.*, 83, 416.
 Forsham, P. H., Thorn, G. W., Bergner, G. E., and Emerson, K., Jun. (1948a): *Amer. J. Med.*, 1, 105.
 —, —, Prunty, F. T. G., and Hills, A. G. (1948b): *J. clin. Endocrinol.*, 8, 15.
 Haines, W. J., et al. (1949): *Fed. Proc.*, Part 1, p. 203.
 Halberg, F. (1949): (To be published.)
 Hellman, L. (1949): *Science*, 109, 280.
 Hench, P. S., Kendall, E. C., et al. (1949): *Proc. Mayo Clin.*, 28, 181.
 —, Slocumb, C. H., et al. (1949): *Ibid.*, 28, 277.
 Hills, G., Forsham, P. H., and Finch, C. A. (1948): *Blood.*, 7, 755.
 Hume, D. M. (1949): *J. clin. Invest.* (in the press).
 Kendall, E. C. (1948): *Vitamins and Hormones*, 6, 278.
 Long, C. N. H. (1947): *Fed. Proc.*, 6, 461.
 Opsahl, J. C. (1949): *Yale J. Biol. Med.*, 21, 255.
 Mason, H. L., Power, M. H., et al. (1948): *J. clin. Endocrinol.*, 8, 1.
 Recant, L., Hume, D. M., et al. (1949): *J. clin. Invest.* (in the press).
 Selye, H., Sylvester, O., et al. (1944): *J. Amer. med. Ass.*, 124, 201.
 Talbot, N. B., Albright, F., et al. (1947): *J. clin. Endocrinol.*, 7, 331.
 Talbott, J. H. (1943): "Gout", Oxford.
 Thorn, G. W., Dorrance, S. S., and Day, E. (1942): *Ann. intern. Med.*, 16, 1053.
 —, and Forsham, P. H. (1949): "Recent Advances in Hormone Research", 4, New York (in the press).
 —, —, Bennett, L. L., et al. (1949): *Amer. J. Med.* (in the press).
 —, —, Prunty, F. T. G., and Hills, A. G. (1948): *J. Amer. med. Ass.*, 137, 1005.
 Vogt, M. (1945): *J. Physiol.*, 104, 60.

REVISION CORNER

FLATULENCE AND THE USE OF CARMINATIVES

"Brother, we await your belch."

BEFORE discussing the carminatives and their use in relieving the symptoms of flatulence, it is necessary to review the mechanism involved in the production of gas in the stomach and intestines. These are by no means well understood and present a problem in research fraught with many practical difficulties.

It should be noted that the term "wind" is used somewhat indiscriminately by patients to describe a variety of visceral sensations. It is used not only to describe belching and the excessive passage of flatus per rectum, but also for sensations of intestinal fullness whether due to flatulence or not; occasionally the pain of serious organic disease, such as cardiac pain or the pain of gastric or duodenal ulcer, masquerades under the guise of "wind". It is therefore not advisable to accept the patient's complaint of "wind" as necessarily correct, and further questioning is often required to discover what really is meant.

A certain quantity of gas is normally present in the stomach and intestines. The gas bubble in the fundus of the stomach is physiological and symptomless. Not infrequently at the screening of patients an individual is found in whom a large collection of air is constantly found with entire absence of symptoms, and conversely, in patients with complaints of gastric flatulence a comparatively small quantity may be present. Much the same applies to the colon also. There is therefore no fixed line at which the amount of gas becomes pathological, and flatulence is best defined as the presence of gas in the stomach or intestines, the passage of which, either upwards or downwards, causes relief of symptoms. In practice, a fairly sharp distinction can be drawn between gastric and intestinal flatulence.

GASTRIC FLATULENCE

Apart from cases of pyloric obstruction when gas may be produced by fermentation in the stomach, the cause of gastric flatulence is always aerophagy. A small quantity of air is normally swallowed with food and drink and is unostentatiously returned postprandially. Deglutition is, however, a complicated neuromuscular feat which is only mastered after considerable practice. Babies are manifestly poor executants, swallowing large quantities of air with their food, and it is a matter of observation that a few adults have never learnt to swallow neatly, and these individuals are liable to suffer from gastric flatulence after food which is promptly relieved by eructation. A small minority of these individuals have in addition never acquired the facility of eructation, and it is in these patients, swallowing air in large quantities and unable to rid themselves of it, that the rare condition described by Hurst in this country as "aerogastric bloquée" occurs, manifested by severe pain, gastric distension and sometimes visible peristalsis, and relieved immediately by passage of a stomach tube.

Aerophagy at times other than meal times is a common symptom of many gastrointestinal diseases. Gall-bladder disease is classically associated with "flatulent dyspepsia", but it is less often appreciated as a common symptom of many other conditions, for example, gastric and duodenal ulcer, carcinoma of the stomach, hiatus hernia, short œsophagus, and carcinoma of the œsophagus. It is, in fact, true that any condition giving rise to pain or discomfort in the epigastrium or substernal region may be associated with aerophagy. It is for this reason that gastric flatulence so often occurs together with anginal pain or the pain of cardiac infarction.

Finally, aerophagy may be entirely a neurotic symptom. In some of these cases the aerophagy begins innocently enough in an attempt to relieve a trivial epigastric

hormone (ACTH). The status of the adrenal cortical function in 21 patients with rheumatoid arthritis has been ascertained and found to be essentially normal in 18 of the patients. There appears to be a wide variation in the state of adrenal cortical function from patient to patient, without apparent correlation with the severity or manifestations of the disease. In 9 patients with rheumatoid arthritis in whom pituitary adrenocorticotrophic hormone was capable of stimulating the adrenal cortex to increased activity, there was striking clinical improvement and a reversal of abnormal laboratory findings. Three patients with rheumatic fever and two patients with disseminated lupus erythematosus were similarly improved by ACTH therapy, as was one case of gout.

With the present inadequate supply of synthetic compound E acetate and pituitary ACTH, non-specific methods for stimulating an intact pituitary-adrenal system and naturally occurring adrenal cortical extracts have been tried with variable success in the treatment of rheumatic diseases.

Associated in these studies were Dr. Peter H. Forsham and Dr. S. Richardson Hill, Jun., of the Peter Bent Brigham Hospital. Dr. J. Sydney Stillman and Dr. Stephen Smith III, of the Robert Breck Brigham Hospital, and Dr. Joseph E. Warren of The House of The Good Samaritan; all of the Department of Medicine, Harvard Medical School, Boston, Mass.

References

- Albright, F. (1942-43): *Harvey Lect.*, 38, 123.
 Conn, J. W. (1948): *Arch. intern. Med.*, 83, 416.
 Forsham, P. H., Thorn, G. W., Bergner, G. E., and Emerson, K., Jun. (1948a): *Amer. J. Med.*, 1, 105.
 —, —, Prunty, F. T. G., and Hills, A. G. (1948b): *J. clin. Endocrinol.*, 8, 15.
 Haines, W. J., et al. (1949): *Fed. Proc.*, Part 1, p. 203.
 Halberg, F. (1949): (To be published.)
 Hellman, L. (1949): *Science*, 109, 280.
 Hench, P. S., Kendall, E. C., et al. (1949): *Proc. Mayo Clin.*, 28, 181.
 —, Slocumb, C. H., et al. (1949): *Ibid.*, 28, 277.
 Hills, G., Forsham, P. H., and Finch, C. A. (1948): *Blood.*, 7, 755.
 Hume, D. M. (1949): *J. clin. Invest.* (in the press).
 Kendall, E. C. (1948): *Vitamins and Hormones*, 6, 278.
 Long, C. N. H. (1947): *Fed. Proc.*, 6, 461.
 Opsahl, J. C. (1949): *Yale J. Biol. Med.*, 21, 255.
 Mason, H. L., Power, M. H., et al. (1948): *J. clin. Endocrinol.*, 8, 1.
 Recant, L., Hume, D. M., et al. (1949): *J. clin. Invest.* (in the press).
 Selye, H., Sylvester, O., et al. (1944): *J. Amer. med. Ass.*, 124, 201.
 Talbot, N. B., Albright, F., et al. (1947): *J. clin. Endocrinol.*, 7, 331.
 Talbott, J. H. (1943): "Gout", Oxford.
 Thorn, G. W., Dorrance, S. S., and Day, E. (1942): *Ann. intern. Med.*, 16, 1053.
 —, and Forsham, P. H. (1949): "Recent Advances in Hormone Research", 4, New York (in the press).
 —, —, Bennett, L. L., et al. (1949): *Amer. J. Med.* (in the press).
 —, —, Prunty, F. T. G., and Hills, A. G. (1948): *J. Amer. med. Ass.*, 137, 1005.
 Vogt, M. (1945): *J. Physiol.*, 104, 60.

hard faeces is certainly a most uncommon cause of flatulence. There is no doubt, however, as to its frequent association with a redundant colonic loop, and here kinking of the bowel probably plays a part, although not the whole part, since deficient absorption from venous congestion is also likely to be present in such cases.

THE CARMINATIVES

These drugs belong to the group of volatile oils given for the purpose of aiding the expulsion of gas from stomach and intestines. Pharmacologically they act, when taken internally, mainly by increasing peristalsis and relaxing sphincter tone. They are in fact gastro-intestinal irritants and act violently as such if taken in large doses. They are mildly antiseptic, but it is not to be anticipated that this property will have great effect in reducing intestinal fermentation. These actions are not particularly striking, and if these were all it is doubtful if the carminatives would have retained their popular reputation throughout the centuries. They do, however, directly stimulate the mucosa of the mouth, pharynx and œsophagus, and produce in so doing a pleasing sensation of warmth from lips to cardia. This may be described as a counter-irritant action, and taken postprandially when discomfort due to gastric flatulence is present they are undoubtedly effective in relieving to some extent the sensation of fullness. Relaxation of the cardia may also assist in the physiological expulsion of excess swallowed air from the stomach. Their efficiency in flatulence distal to the pylorus is far more uncertain, but by promoting peristalsis they probably do assist to some extent in the expulsion of gas from the colon.

Somewhat overshadowed by the powerful and specific drugs of the twentieth century the carminatives should nevertheless retain their place in everyday therapeutics, although reflection on the numerous mechanisms involved in the production of intestinal gases will show that their efficiency in its control is limited.

G. D. HADLEY, M.D., F.R.C.P.

ACUTE RETENTION

ACUTE retention of urine is an urgent condition requiring a clear conception of the etiological factors involved and the possibilities and consequences of methods adopted for its relief. As a surgical emergency it is only less serious than its counterpart, acute intestinal obstruction, on account of the bladder being naturally more accommodating and not being exposed to the same risks of inviability. At the same time, owing to the distressing nature of the condition and the subsequent danger of waste products accumulating in the body, immediate treatment must be regarded as imperative. Unfortunately, the advocacy of various methods for its relief has led to some confusion in the minds of those called upon to deal with the condition as an emergency. Briefly, such perplexity may be ascribed to the following causes: difficulty in distinguishing between acute and chronic retention; failure to appreciate the significance of the underlying causes; a tendency to dogmatism on the part of urologists dealing with a particular type of case; and modern developments in the field of prostatic surgery which demand special preparation for their success.

The essential difference between acute and chronic retention depends, as the latter adjective implies, upon the time taken for occlusion to become absolute, and fortunately a corresponding difference in the symptomatology and clinical signs is usually apparent. In acute retention rapid filling of the bladder leads to an urgent and painful, although fruitless, desire to micturate, and the distended viscus becomes palpable as a tense and tender swelling arising out of the pelvis. These findings are distinct from those resulting from the more gradual accumulation of residual urine met with in chronic retention, in which overdistension of the bladder fails to excite painful sensations, and the viscus, although often larger, feels like a relatively inelastic bag filled with water—which indeed it is. Whereas in acute retention no urine can be passed, in the chronic condition it is not unusual for small

discomfort and persists as a habit long after the original cause has disappeared. Aerophagy as a neurotic symptom is usually frequent, unrelated to meals, and noisy. It is sometimes a greater embarrassment to the patient's family than to himself. Indeed, Cohen cites the case of an unbalanced individual with solitary propensities who utilized his aerophagy to rid himself of his unwanted friends. Often, however, the patient himself is genuinely distressed and anxious about his symptom, which is ascribed by him to fermentation in the stomach. Close observation of these patients generally shows that the air never reaches the stomach in any quantity. It is noisily sucked or swallowed into the œsophagus and immediately regurgitated. Gastric distension is seldom a feature of these cases.

INTESTINAL FLATULENCE

Apart from the rare cases of "aerogastric bloquée" it is unlikely that any considerable quantity of air passes through the pylorus. Excess gas in the intestines, apart from intestinal obstruction, is for practical purposes nearly always in the colon. It may be caused by: (1) excessive production of gas by fermentation; (2) defective absorption; (3) increased secretion; (4) defective elimination.

The conditions for excessive gas production are most favourable in the right half of the colon and it is here that most of the gas is produced. The gas has two main sources: the bacterial decomposition of cellulose and the fermentation of carbohydrates. The former probably always takes place to a certain extent; it is increased by a high cellulose content of the diet and possibly sometimes by an abnormal bowel flora. The latter is abnormal, since at ordinary rates of intestinal transit the amount of fermentable carbohydrate reaching the colon is small. It may, however, be increased if the carbohydrate content of the diet, particularly the starch content, is very high, and it is increased if there is any marked degree of small intestinal hurry. It is therefore much more likely to be associated with diarrhœa than with constipation. Although there is a tendency to-day to regard the existence of carbohydrate dyspepsia with suspicion, there is no doubt that the condition exists. Prisoners of war in Europe during the last war are familiar with the enormous quantities of bowel wind generated by a really high potato diet.

A variable but probably considerable quantity of gas is absorbed from the bowel and exhaled from the lungs. The amount is impossible to calculate, but in the herbivora it is known to be very large indeed. It is to be expected therefore that any condition in which there is venous congestion of the bowel will lead to intestinal flatulence. Thus it is often a marked feature of cirrhosis and of congestive cardiac failure. Inflammatory conditions of the mucosa may similarly be a cause, e.g. ulcerative colitis, and the chronic mild irritation of the colonic mucosa resulting from the prolonged use of purgatives.

Whilst absorption of gas from the bowel has long been known to occur, the reverse—secretion of gas into the bowel—is less easy to demonstrate. It is, however, now an accepted fact that it can and does take place. It is indeed difficult in any other way to account for the sudden large quantities of intestinal gas that appear under certain conditions, the most striking examples being in cases of urteric calculus and during the operation of retrograde pyelography. This gas is often symptomless; it appears within a matter of minutes and may disappear almost equally quickly. It seems likely that its appearance is related to sudden loss of intestinal muscular tone of reflex origin. It is noteworthy that the disappearance of the gas after injection of pituitrin is not usually manifested by expulsion of large quantities per rectum. Most of it is probably reabsorbed, the process being speeded by the increased pressure within the lumen of the bowel due to the action of the pituitrin.

Defective elimination is a less important cause of intestinal flatulence. It may be voluntary. Plugging of the lumen of the colon in severe constipation by a mass of

indwelling catheter or by repeated catheterization in the home or surgery should be condemned, as the risk of infection is high, and the chance of successful operative treatment subsequently reduced. There is therefore no question that in cases of "acute on chronic" retention early transfer to an institution where adequate facilities for investigation and treatment are available is of the utmost importance.

In the remaining cases in which no previous history of urinary difficulty has existed, the practitioner may be more doubtful of the correct course to adopt. It is difficult, on rectal examination at the time of retention, to form an opinion as to the possible obstructing capacity of the prostate, since it is well known that the size and consistency of the gland may be affected by congestion and downward displacement from the weight of a full bladder. Over-allowance for the congestive element may render it tempting to rely on simple catheterization in the home with apparently satisfactory immediate results. It cannot be emphasized too strongly, however, that complete retention is rarely brought about by congestion alone, and that an occult obstructive element with more serious potentialities usually exists. If catheterization is adopted, a covering course of chemotherapy should be prescribed to minimize the risk of infection, and even if apparently normal micturition is restored the case should be subjected to full urological review at an early date. In no circumstances is it justifiable to proceed with hormonal therapy or other palliative measures until complete investigation of the case has been carried out.

J. D. FERGUSON, M.D., F.R.C.S.

NOTES AND QUERIES

Cardiac Failure under Chloroform Anæsthesia

QUERY.—Is there any pharmacological basis or clinical justification for the use of the nitrites in primary cardiac failure occurring under chloroform anæsthesia?

REPLY.—I am not aware of any justification for using nitrites in primary cardiac failure under chloroform anæsthesia. The risk of arrhythmias, particularly ventricular fibrillation, is generally accepted as the main danger. Intravenous quinidine would seem the correct treatment and, in fact, in operations on the heart at Guy's Hospital, even when chloroform is not being used, quinidine is used prophylactically before operation in the attempt to prevent such arrhythmias.

MAURICE CAMPBELL, O.B.E., D.M., F.R.C.P.

Bazin's Disease

QUERY.—I have a patient with erythema induratum (Bazin's disease). I should be most grateful to have advice: none of my textbooks mentions any form of treatment.

REPLY.—Correctly speaking, Bazin's disease is a malady of girls and young women in whom there is evidence of tuberculosis. In these, the treatment is to find the tuberculous focus and remove or cure it. In my experience in this country, so-called Bazin's disease is a malady of middle-aged women with "piano-stool" legs, a sluggish peripheral circulation, and no more

evidence of tuberculosis than most of us can show. For these cases sympathectomy may be considered. Other measures may be summarized as follows: Reduce the patient's weight; tell her that standing about favours the development of the lesions, and so does coldness of the legs. Reasonable exercise, a sensible diet and the application of elastic adhesive bandages are advisable; so also is the wearing of warm stockings. Contrast baths of hot and cold water (which may be taken by the use of two buckets at home), massage, infra-red irradiation, radiant heat, diathermy and galvanic baths all have their uses. Rest in bed may be essential in a severe case. The ulcers may be dressed with cod-liver oil, 10 per cent. in zinc paste, or with non-staining iodine ointment, or with a weak mercurial ointment. Sometimes injections of gold or neoarsphenamine are beneficial.

R. M. B. MACKENNA, M.D., F.R.C.P.

Rapid Loss of Hair in Elderly Patient

QUERY.—The hair of a patient of seventy-four started to fall out a month ago and in brushing her hair each morning it comes off in handfuls. Naturally she is distressed at the prospect of baldness. I cannot account for it, whether it may be due to lack of vitamins or be the sequel to a severe attack of influenza some six months ago. On the whole she enjoys good health for her age, except for twinges of arthritis in the spine and lower limbs, with occasional nocturnal cramp, sometimes severe.

amounts to dribble out at intervals: a state referred to as "overflow incontinence". It is important to realize, however, that the majority of cases of acute retention are determined by sudden congestive changes causing a pre-existing partial obstruction to become absolute, and modification of the clinical features may thus prove confusing. In such instances when there is a history of previous urinary difficulty with inadequate emptying, the supervention of complete obstruction may be referred to as "acute on chronic" retention, and the probability of antecedent impairment of renal function and urinary sepsis must constantly be borne in mind.

ETIOLOGY

With regard to the etiology, the fundamental mechanism of acute retention is represented either by a breakdown of the reciprocal action of the detrusor and sphincteric musculature responsible for normal evacuation of the bladder, or by an incapacity of the detrusor to force urine through an organic obstruction in the lower urinary tract. Whilst the latter is much the commoner, the history and circumstances of the case will generally aid in establishing the cause when an obstructive lesion is insignificant or lacking. In certain neurological conditions, such as anterior poliomyelitis and traumatic lesions of the spinal cord, and also in post-operative and hysterical states, acute retention may supervene as a result of paralysis or incoordination of the affected musculature. In all instances other manifestations of the cause are usually obvious. In other cases the sphincter alone may be involved, as in reflex spasm due to posterior urethritis or painful conditions affecting the perineum and anus, which again can readily be detected. Effective treatment of these conditions is better left to be carried out in hospital, if, in fact, the patient is not already there, and arrangements should be made for conveyance as expeditiously as possible.

In practice, the main difficulty in dealing with acute retention is provided by cases with an obstructive lesion in the lower urinary tract. Omitting traumatic injuries to the urethra the majority of these give a history of impaired micturition, denoting a pre-existing partial obstruction which has become absolute as the result of sudden congestive changes. The most frequent cause is undoubtedly benign prostatic hypertrophy, although less often the condition may arise from fibrous contracture of the bladder neck, prostatic cancer, urethral stricture and other lesions.

TREATMENT

In dealing with the common form due to benign prostatic obstruction the following observations may be helpful. Prophylaxis is important and patients exhibiting mild prostatic symptoms should be enjoined to avoid excesses liable to bring about congestion. Social functions, where pleasurable over-indulgence may, through modesty or inadvertency, lead to procrastination, should be avoided. "A wedding or a festival", or a motor coach drive is fraught with risk for the elderly prostatic, and on cold nights the provision of a bed bottle may do much to mitigate the inconvenience of nocturnal frequency with its attendant risk of neglecting the call.

When, however, retention has occurred, it has to be decided whether the condition can safely be relieved by catheter or other method, and if so, whether subsequent investigation and treatment will be necessary. In cases with an antecedent history pointing to prostatic enlargement there is no doubt that retention is only an incident in the course of the disease and if possible the patient should be removed to hospital forthwith without preliminary instrumentation. If immediate conveyance is impossible, emergency catheterization or suprapubic puncture may be performed, with scrupulous attention to asepsis. It must be emphasized that rapid decompression in these circumstances is not entirely without risk, since it may be followed by profuse hæmorrhage leading occasionally to intractable clot retention with severe impairment of renal function. Any attempt at prolonged drainage through an

PRACTICAL NOTES

Oestrogens and Androgens in Mammary Cancer

A REPORT on the results obtained in 105 female patients with advanced inoperable mammary cancer, to whom endocrine substances were administered for one month or longer, is given by F. E. Adair *et al.* (*Journal of the American Medical Association*, August 13, 1949, 140, 1193). Testosterone propionate was given intramuscularly, three times weekly in dosage of 100 mg., to 70 patients with metastases to bone, soft tissue or both. There was objective improvement in 19 per cent. of 48 patients with skeletal metastases, and in 15 per cent. of 54 patients with extra-skeletal metastases. The cumulative dosage at the time of improvement was 500 to 11,400 mg. of testosterone propionate. The improvement, chief among which was the marked relief of pain, lasted for from two to eleven months. Symptomatic improvement was noted in patients even though the disease was at the same time progressive. To a group of 35 patients oestrogenic substances (diethylstilboestrol, ethinyl oestradiol and oestrone sulphate) were given. There was objective improvement in 23 per cent. of those with extra-skeletal metastases, but no favourable effects in those with osseous metastases. The cumulative dose of diethylstilboestrol at the time of improvement was from 210 to 1,470 mg. The improvement lasted for from two to seventeen months. Side-effects from androgen therapy were increase in weight, oedema of the lower extremities, hirsutism and acne. No clinical or laboratory evidence was obtained in any case that either the primary or metastatic mammary cancer had been accelerated by androgen therapy, but acceleration of growth of mammary cancer was observed in one patient treated with oestrogens. A further report on the use of hormone therapy in advanced cancer is given by F. E. Adair in the *Proceedings of the Royal Society of Medicine* (July 1949, 42, 468) in which he discusses improvement after cessation of hormone therapy. In a group of 8 patients who had been treated with androgen for from ten to twenty-four months, receiving total dosages of 12,000 to 19,000 mg., a second period of improvement was demonstrated in 6 cases, all of which had been off therapy for at least two months.

X-ray Treatment of Hyperhidrosis

ON the basis of their experience in 122 patients J. Borak and his colleagues (*Archives of Dermatology and Syphilology*, June 1949, 59, 644) "believe that, properly applied, roentgen

therapy is the best method of treating hyperhidrosis". The age of their patients ranged from fourteen to forty-one, and 71 per cent. were under the age of thirty when first treated. Sixty-two per cent. of them were blonds. From two to eighteen years have elapsed since the completion of treatment in each patient. "All patients have shown pronounced improvement . . . For a large number . . . the results were so satisfactory that no further treatment appeared necessary". In none of the patients was there any evidence of injury to the skin as a result of the treatment. Excessive dryness of the irradiated areas was avoided by discontinuing treatment after 75 per cent. improvement was obtained. Filtered rays were used, and it is stated that no more than two series of treatments should be given. The absence of X-ray injury to the skin is attributed to the use of filtration. In the view of the authors, the use of unfiltered rays is the most important cause of failure in this form of treatment of hyperhidrosis.

Prevention of Gonorrhœa with Penicillin Tablets

A STUDY to test the efficacy of penicillin tablets, taken by mouth, for the prevention of gonorrhœa has been carried out by H. Eagle *et al.* (*Journal of the American Medical Association*, July 16, 1949, 140, 940). Military personnel were used for the test, being divided into two groups, one receiving penicillin tablets and the other placebo tablets containing no penicillin. Penicillin G was used for the study, initially a single 100,000 unit tablet being issued to the men on return from shore leave, whether or not there had been exposure to infection. Later the dosage was increased to 250,000 unit tablets. With the initial dosage of 100,000 unit tablets there were 5 cases of gonorrhœa in 3,218 liberties, in 3 of which it was doubtful if the penicillin tablet had been taken, this group consisted of 151 to 213 men. When the dosage of the tablet was increased to 250,000 units, there was only one case in 87 to 141 men with 569 liberties, and the man denied having received a tablet. In a control group of 176 to 195 men receiving placebo tablets there were 43 cases of gonorrhœa in 3,616 liberties in a twenty-four week period. An estimate of the over-all incidence after withdrawal of penicillin showed 46 cases of gonorrhœa in 4,920 liberties during sixteen weeks (total number of men 265-303). Penicillin was then made available to the entire station on a voluntary basis, so that it was taken only by

REPLY.—There are three main possibilities of a sudden hair fall in a patient aged seventy-four:—

(a) *Symptomatic of debility*, intercurrent illness, or general disease such as anæmia, or as a result of fatigue as may occur with long-continued nervous strain. Six months is perhaps a little outside the usual time limit for a convalescent alopecia after influenza. The whole root of the hair may be seen attached to the hair in such alopecia.

(b) *Senile seborrhœa*, due possibly to some endocrine alteration in balance or in the œstrogen-androgen ratio, may produce rapid alopecia. Seborrhœic "dandruff" should be present with general scaling of the ears or scattered areas of scaling which may resemble psoriasis behind the ears or on the scalp. Such seborrhœic states may be influenced by inadequate diet or unbalanced diet with excessive carbohydrate, lack of protein and vitamin B complex. Injections of crude liver, 4 ml. of "plexan" or "campolon", may be given twice a week. Anxiety which may be *post* or *propter hoc* will aggravate, and phenobarbitone, $\frac{1}{4}$ of a grain (16 mg.) t.d.s., usually helps the older patient. Thyroid may also be tried.

Locally, use ointment of salicylic acid and sulphur N.F., or with tar added ("pragmatar": Menley & James). The latter is tested on a small area to exclude sensitivity. Œstrogens locally, such as dienœstrol ointment (B.D.H.), can be tried.

(c) *Alopecia areata*.—Small round patches may be seen among the areas losing hair, and the hairs may be depigmented and exhibit the exclamation mark appearance where they break off short. Rapid alopecia may occur.

General management requires massage of the scalp at night, brushing of the hair, and the use of a soapless shampoo fortnightly. If ultraviolet light is contemplated, exposures must be very gently graduated, as the senile skin does not tolerate it well.

GEOFFREY HODGSON, M.B.E., D.M.

Trilene Anæsthesia

QUERY.—I have used a Cyprane inhaler, and find that analgesia can be obtained thereby, but not anæsthesia. What type of inhaler should be used for trilene?

REPLY.—The Cyprane inhaler is designed to give analgesia only, but with a susceptible patient it is possible under certain conditions to produce full anæsthesia. The best apparatus for producing anaesthesia with trilene is the Freedman bottle, and for anæsthesia, Marrett's apparatus is most suitable. It must, however, be realized that evidence is accumulating to

show that trilene is not without danger in expert hands, and when it is being used for anæsthesia, the administrator must be qualified to accept full clinical responsibility for the patient's welfare throughout the administration of the anæsthetic.

A. W. HIND, M.B., B.S., D.A.

Carbon Dioxide in Asthma

QUERY.—Is the use of carbon dioxide of any value in the treatment of asthma? If it is, I should be glad of information concerning the amount that should be used and how often it can be given. Are there any toxic effects?

REPLY.—Despite recent reports in the popular press, carbon dioxide has no specific action in the treatment of asthma. It is, however, of some use in the disease by reason of the fact that it enforces deeper and more active respiratory movements, thereby encouraging the evacuation of sputum from the peripheral bronchioles. There is also some evidence that the gas aids the liquefaction of sputum and increases the absorptive power of the bronchial mucosa. It is given in a strength of 5 to 10 per cent. carbon dioxide in oxygen, for three to five minutes hourly, by means of a B.L.B. mask or by Tudor Edwards' spectacles. There are no toxic effects.

C. ASTLEY CLARKE, M.D., F.R.C.P.

Refusal of Food in Childhood

QUERY.—A child, aged three years, has complete negativism for food, so much so that he tries to run away or cry when asked to take his usual feeds. If forced to take food, he generally vomits it. Frequent variation in food has no effect, and the child has total disinclination for food of any description. He looks and feels quite healthy, and is very active.

REPLY.—The refusal of food is evidently not at present injuring the child's health. Removal of the parents' anxiety is important. The child should be given food at regular intervals. He should have a short period of rest before his meal to avoid excitement, and should then be left alone for half an hour with his food. If he has ever expressed a preference for one type of food between meals, this may be introduced into his regular meals. It is good policy at first to give relatively small portions, for the battle is half-won should the child ask for more. The parents should be reassured that no harm will be done even if he appears to refuse several meals in all. If emotional tension is removed from the home, and if it is quite certain that no physical illness is present, the child will start to eat with the regime described above.

A. SPENCER PATERSON, M.D., F.R.C.P.

into any one of the three positions according to which fluid is to be injected, being so designed that it is impossible for fluid to flow through more than one inlet to the outlet arm at any time. Advantages claimed for the connector are

- 1) it provides an easily sterilized and operated apparatus for intravenous administration of three different solutions through one needle,
- 2) it is impossible for either pentothal sodium or curare solutions, when being injected, to back-flow into the tubing from the vacoliter with consequent dilution and delay in administration of the solution

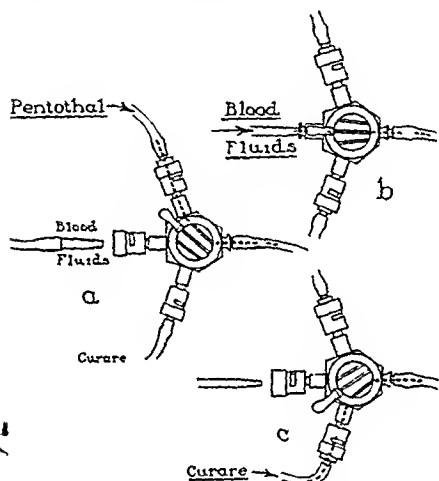


FIG. 1—Four way connector for the simultaneous administration of pentothal sodium, curare and fluids or blood

Etiology of Erythema Nodosum

In a clinical and radiological investigation of 124 cases of erythema nodosum, J. H. Middlemiss (*British Journal of Radiology*, July 1949, 22, 375) found that 55 had radiological evidence of active tuberculous disease of the lungs. Forty-nine of these were associated with primary tuberculous infection. Assessing the radiological findings in conjunction with the Mantoux reactions, 99 cases (77.3 per cent) were regarded as 'being probably of tuberculous origin'. In eight cases there was a history of the eruption appearing after the administration of sulphonamides, three of these had some causal relationship to tuberculosis. In several cases fresh crops of the eruption were produced by the administration of sulphonamides. In four cases haemolytic streptococci were cultured from throat swabs, whilst in 15 cases no definite etiological factor could be found. It is concluded that "in England the possibility of primary tuberculosis must be considered in all cases of

erythema nodosum until some other etiological factor is demonstrated or proven. In all cases, tuberculous or non-tuberculous, the evidence points towards the eruption being a non-specific allergic phenomenon."

Tridione in the Treatment of Minor Epilepsy

The results of treatment with tridione (3, 5, 5-trimethylvaldimine-2, 4-dione) in 45 cases of minor epilepsy are recorded by G. R. Davies and J. D. Spillane (*Brain*, June 1949, 72, 140). Many of the patients had major epilepsy as well as minor epilepsy. The initial dose was usually one capsule (0.3 g) thrice daily, and in the majority of patients this proved to be the optimum dosage. The maximum dose used was 0.6 g thrice daily. "Patients who showed the most satisfactory response to tridione in no case required more than 0.3 g four times daily". In many cases it was possible to reduce the maintenance dose to as little as 0.1 g daily. Satisfactory results were obtained in 38 patients, five patients were improved, and in two the drug was ineffective. Both the failures had severe major epilepsy as well as minor epilepsy. Three "side-effects" have been reported with tridione: photophobia, skin eruptions, and disturbance of blood cell formation. Photophobia occurred in 11 patients (22 per cent), in the majority it cleared up spontaneously without cessation of treatment. Three patients developed a severe skin reaction necessitating cessation of treatment. Subsequently it was found possible to re-institute treatment with tridione in all three without any harmful effect. Apart from transient eosinophilia, no effect was found on the white blood cell count in this series. It is concluded that tridione is "the most effective substance as yet available for the treatment of minor epilepsy."

Urine Sugar Test for the Blind Diabetic

A simple test, which it is claimed can be carried out by a blind patient unaided, is described by E. P. Covey (*American Journal of Clinical Pathology*, May 1949, 19, 500). A little fresh, active yeast is placed in a plastic or metal vial, which is then filled with urine. A rubber finger cot is clipped over the mouth of the vial to come in contact with the urine, and is secured with a rubber band. The specimen is allowed to stand at room temperature. If sugar is present, fermentation takes place within ten to thirty minutes and causes the finger cot to bulge. With increasing experience the amount of sugar can be judged roughly by the degree of tension and bulging.

those who had actually been exposed. The incidence figure was: "1 questionable case in 1,454 liberties followed by penicillin prophylaxis".

Penicillin in Gonorrhœal Arthritis

A REPORT of the results obtained in a series of twenty-eight cases of gonorrhœal arthritis treated with penicillin is given by N. Spitzer and O. Steinbrocker (*American Journal of the Medical Sciences*, August 1949, 218, 138). The dosage of penicillin varied from 0.5 million units to 9.3 million units, according to the severity of the case, and the duration of treatment varied from three to thirty days. In twenty-three cases diagnosis was based on clinical findings and on the determination of definite gonococcal infection in the genito-urinary tract; in five cases cultures were obtained from the joint fluid by aspiration. Aspiration was not carried out when the arthritis was limited to the small joints of the extremities or inaccessible articulations. Cure, i.e. complete restoration of the joints, was obtained in 8 cases; great improvement in 15, in the form of quick subsidence of the fever and disappearance or alleviation of the signs of acute joint inflammation; failure in 5 cases. It is stressed that measures to preserve joint function and to overcome impending contractures should be instituted early as supplements to penicillin therapy. Finally, it is stated: "Penicillin effected a bacteriologic cure in every patient, according to the clinical course".

Oral Penicillin in the Treatment of Pneumonia

A COMPARISON of the effects in pneumococcal pneumonia of intramuscular and oral penicillin is reported by W. W. G. MacLachlan and his colleagues (*Canadian Medical Association Journal*, August 1949, 61, 134). Orally, penicillin was given as the calcium salt in tablet form, each tablet containing 100,000 units. One tablet was given every hour for six hours and then every two hours for eighteen doses: i.e., a total dosage of 2,400,000 units. Intramuscularly, the total dosage of penicillin was 500,000 units. The type of pneumonia treated in this series was said to be a particularly severe one: with a high incidence of bacteriæmia, many chronic alcoholics, a poor physical type of patient, and about 20 per cent. of the patients over the age of sixty. There were no children under the age of fifteen years. Of the 75 patients treated with intramuscular penicillin, 90.7 per cent. recovered, compared with 91.7 per cent. of the 74 patients receiving oral penicillin. Even more striking is the fact that the recovery rate among

the 19 patients with bacteriæmia treated with intramuscular penicillin was 84.2 per cent., compared with a recovery rate of 89.7 per cent. among the 29 bacteriæmia cases treated with oral penicillin. Among the 29 patients in whom penicillin blood levels were estimated, the average blood level one hour after 100,000 units by mouth was 1.60 units per ml. of serum, whilst two hours after administration it was 1.09 units per ml.

Fluorine and Dental Caries

"THE result of clinical investigations upon large numbers of children at an age when the caries incidence rate is high . . . leaves no doubt that the topical application of fluorides reduces the overall caries incidence . . ." writes G. J. Parfitt (*British Dental Journal*, August 5, 1949, 87, 53). A 2 per cent. sodium fluoride solution in distilled water is employed. After cleansing with a motor driven rubber cup and fine pumice paste, the teeth are isolated with cotton-wool rolls, one half of the mouth being done at a time. The teeth are then dried with compressed air, and the fluoride solution applied to the surfaces with a cotton swab, first on the labial and buccal surfaces, and then on the occlusal and lingual surfaces. The solution is allowed to dry in air for four minutes. The patient should wash the mouth after each of the four applications. The treatment is recommended to be done twice weekly, with three- or four-day intervals, up to a minimum of eight treatments. It is stated that "although fluorine is a toxic substance, its use, in the strengths and amounts recommended, is without danger to the patient". Knutson (*U.S. Pub. Hlth. Rep.*, 1943, 58, 47), upon whose work the above regime is based, reported a 40 per cent. reduction in caries incidence in a group of 289 children between the ages of seven and fifteen, treated by the method.

Four-Way Connector for Simultaneous Intravenous Administration

A FOUR-WAY connector designed for the simultaneous administration of pentothal sodium, curare, and fluids or blood is described by R. F. Courtin and J. S. Lundy (*Proceedings of the Staff Meetings of the Mayo Clinic*, August 3, 1949, 24, 419). The connector has three inlet arms, and one outlet arm connected by a short piece of rubber tubing to the needle which has been inserted in the vein. The three inlet arms are connected by rubber tubing to (a) the pentothal sodium syringe; (b) to the curare syringe; and (c) to a vacoliter containing either fluid or blood. If the third arm is not required, a small sterile cap is placed over it. A tap is fitted at the intersection of the arms, which can be turned

valuable addition to the literature of surgical infections. It could have been written only by a man whose training makes him at home equally in ward and laboratory, and who comes from an institution where full records and accurate statistics are an essential part of the organization. Opening with a short chapter on the physiological principles underlying the reaction of the body to infection, and paying tribute to the work of Fleming, Colebrook and Florey, the author treats his problem system by system, in each instance beginning with a brief historical note, followed by the pathology, bacteriology, signs, symptoms and treatment of the condition under discussion, and a series of carefully documented case reports. To anyone seeking help in a difficult case, these reports will prove most helpful, since they cover almost every vagary of infection, including such universally puzzling conditions as subphrenic abscess, spinal, epidural, and subdural suppuration, gangrene resulting from occlusive vascular disease, and his own particular contribution—progressive postoperative bacterial synergistic gangrene. The book is well produced with good print on good paper, illustrated by clear photographs and self-explanatory diagrams.

B.C.G. Vaccination in Theory and Practice.

By K. NEVILLE IRVINE, D.M., B.Ch.
Oxford: Blackwell Scientific Publications, 1949. Pp. xiii and 130. Price 9s. 6d.
Now that the Ministry of Health is introducing B.C.G. vaccination into this country, practitioners need a concise review of the subject. This book provides such a survey, with over 500 references to the literature; theoretical aspects, production problems, and the important questions of virulence and safety are gone into thoroughly. The evidence is marshalled to show that since 1930 no evidence has been put forward to question the safety of the vaccine. Full descriptions of the various techniques of vaccination and re-vaccination are included, and also a summary and discussion in which the reader is given the benefit of eighteen years' impartial observation by the author. One agrees with the foreword by Dr. Birkhaug (New York State B.C.G. Laboratory) that here is indeed a timely and valuable monograph, which should be in the hands of all those interested in B.C.G.

Diseases of the Warm Climates. By ALBERT DUBOIS, M.D., and L. VAN DEN BERGHE, M.D., D.Sc. London: William Heinemann (Medical Books) Ltd., 1949. Pp. xv and 445. Figures 99. Price 42s.

The authors of this new work have behind them many years of experience in the Belgian Congo

and at the Institute of Tropical Medicine at Antwerp. They have written a concise and up-to-date book which covers the whole field of tropical medicine. Two editions have been published—in French and in English. Unfortunately the translation into English leaves much to be desired and will need careful revision when a further edition is prepared. The book is a good practical guide to diagnosis and treatment. It is attractively arranged and well produced with excellent illustrations.

NEW EDITIONS

A Synopsis of Medicine, by Sir Henry Tidy, K.B.E., M.D., F.R.C.P., in its ninth edition (John Wright & Sons Ltd., 30s.) has been subjected to complete revision for the inclusion of the many advances since the appearance of the previous edition in 1945.

A WEALTH of new material has been added to *Diseases of Women*, by Ten Teachers, edited by Clifford White, M.D., F.R.C.P., F.R.C.S., F.R.C.O.G., Frank Cook, F.R.C.S., F.R.C.O.G., and Sir William Gilliatt, K.C.V.O., M.D., M.S., F.R.C.P., F.R.C.S., F.R.C.O.G., in its eighth edition (Edward Arnold & Co., 25s.), and the chapter on the endocrine glands has been entirely rewritten. This work is too well known for detailed criticism, but the new edition will be found up to date in all sections.

Fractures and Dislocations in General Practice, by John Hosford, M.S., F.R.C.S., revised in its second edition by W. D. Coltart, F.R.C.S. (H. K. Lewis & Co. Ltd., 21s.) has been extensively revised to incorporate advances since the appearance of the first edition in 1939. The main feature of the book, however, has been maintained, i.e., a clear and practical exposition of the treatment of fractures for the general practitioner and the senior student of surgery.

The Science and Art of Joint Manipulation. Vol. 1. The Extremities, by James Mennell, M.D., B.C., in its second edition (J. & A. Churchill Ltd., 24s.) contains some new or alternative methods of manipulation of the shoulder joint and of the cuboid, and a number of new illustrations, which bring the total up to 299.

In the preparation of the sixth edition of *Diseases of the Nervous System*, by F. M. R. Walshe, M.D., D.Sc., F.R.S. (E. & S. Livingstone Ltd., 17s. 6d.) the chapter on neurosyphilis has been rewritten and a detailed description of penicillin therapy included. The use of this drug in the treatment of meningitis, a brief mention of streptomycin therapy in tuberculous meningitis, and extensions of the sections on intracranial abscess and acute poliomyelitis are among the additions to this well-known textbook.

REVIEWS OF BOOKS

A Companion in Surgical Studies. BY IAN AIRD, CH.M., F.R.C.S. Edinburgh: E. & S. Livingstone Ltd., 1949. Pp. viii and 1060. Price 63s.

THIS is a volume of outstanding merit which will serve as a book of reference to all practicing surgeons. The modern tendency has been to produce books of multiple authorship, each writing on his own subject and seeking the aid of numerous illustrations. This book, however, is a return to the older type of textbook, in which a single author presents a balanced review of the whole subject. The author apologizes for this, and yet he has succeeded in producing a book which will have an immediate appeal. Each subject is dealt with in its due proportion, original articles are referred to, the author offers criticism as a result of his own personal experiences, and has thus succeeded in writing a broad review of modern surgery. The illustrations will not be missed. Anyone seeking information on a subject would be well advised in the first place to consult this volume and then to read the original articles referred to. It would be superfluous to attempt to criticize this book in detail. It is a masterpiece of clear exposition by an author of remarkable breadth of view, to whom congratulations are offered for having successfully filled a long-felt want.

British Surgical Practice. Vol. 4 and 5. EDITED BY SIR ERNEST ROCK CARLING, F.R.C.P., F.R.C.S., and J. PATERSON ROSS, M.S., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1949. Pp. xxvii and 518; xxvii and 532. Figures 483 and 220. Price 60s. per volume.

WITH each succeeding volume of this magnificent work, the excellence of the articles, the abundance and fine rendering of the illustrations, and the superb production, excite increasing admiration, and the folly of the general arrangement becomes more apparent.

Volumes 4 and 5, like their predecessors, contain many helpful contributions from physicians and pathologists, of which those on "Fibrositis" by Copeman, on the "Reticuloses" by Hadfield, on "Hormones" by Bishop, and on "Lupus" by Dowling and Macrae, deserve special mention. The surgical articles are all good: some of them, e.g., those on "Faciomaxillary Injuries and Deformities" by Mowlem, on "Fistula in Ano" by the St. Mark's surgeons, on "The Hand" by Barron, on "Epilepsy" by Penfield, on "Diaphragmatic Hernia" by Dunhill, and on "Surgical Diseases

of the Larynx" by Ormerod, are classics.

The alphabetical arrangement of an Encyclopædia is quite unsuited to a work on surgery. Which is the important word, the adjective or the noun?; in volume 4 we have Focal Epilepsy under F, yet Diaphragmatic Hernia under H. Cleft Palate is entirely hidden, until the general index comes out, under Facio-Maxillary injuries and deformities. "Glottis, œdema of" has been marooned in Volume 4 away from "Larynx, disease of" in Volume 5, and Glaucoma is separated from most of the other eye diseases under E and the diseases of the lens under L. The surgeon wishing for information on a joint is uncertain whether to consult "Arthritis" in Volume 1 or "Joints, injuries and disease" in Volume 5; in the pathology of inflammation he has to flit from "abscess" in Volume 1 to "infection" in Volume 5. That the publishers have qualms is suggested by the grouping of all fractures in one article under F and of most kidney lesions under K, but Aird, writing a chapter on "The Intestines" in Volume 5 that is otherwise comprehensive, has his style cramped because Edwards has already stolen his "Diverticula" in Volume 3. These are criticisms of the policy of the publishers, and most of them will be met when the comprehensive index appears.

Text Book of Surgery. By P. KIELY, M.D., B.Sc., M.Ch., F.R.C.S. London: H. K. Lewis & Co. Ltd., 1949. Pp. ix and 1184. Figures 611. Price 45s.

THIS book, which covers the whole field of surgery, is based upon the author's lecture notes and digests of modern standard works. It is comprehensive, but suffers from the defects of this method of construction. Lecture notes and precis lack the colour of the original. Some sections, notably those on tumours and fractures, are excellent; others, such as that on gangrene and burns, do not reflect modern surgical practice. Professor Kiely, a general surgeon in the full sense of the word, has produced a book which, if it does not dwell upon the principles of surgery, covers the field and should be of great value to senior students and those recently qualified.

Clinical Aspects and Treatment of Surgical Infections. BY FRANK L. MELENEY, M.D., F.A.C.S. Philadelphia and London: W. B. Saunders Company, 1949. Pp. xiii and 840. Figures 287. Price 60s. DR. MELENEY is to be congratulated on a most

THE GENERAL ADAPTATION SYNDROME AND THE DISEASES OF ADAPTATION

By HANS SELYE, M.D.

*From the Institute of Experimental Medicine and Surgery, University of Montreal,
Canada.*

EXPERIMENTAL and clinical observations have shown that in addition to the specific adaptive reactions (e.g. serological reactions to specific antigens, muscular hypertrophy subsequent to physical work, proliferation of the epidermis where the skin is exposed to pressure or friction), there are certain physiological mechanisms which help to raise resistance to damage as such. The endocrine system plays a prominent part in these latter reactions, which occur irrespective of the specific nature of the evocative damaging agent.

The sum of all those non-specific, systemic reactions of the body which ensue upon long-continued exposure to stress has been termed the "general adaptation syndrome". It is characterized by a number of morphological and functional changes. Among the most prominent of these are: enlargement of the adrenal cortex with increased corticoid-hormone secretion, involution of the thymus and of other lymphatic organs, gastro-intestinal ulcers, certain metabolic changes and variations in the resistance of the organism.

If an individual is continuously exposed to stress, the resulting general adaptation syndrome evolves in three distinct stages:—

(1) *The alarm reaction*, which is defined as the sum of all non-specific systemic phenomena due to sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted. Some of these phenomena are only passive and represent signs of damage or "shock", e.g. hypothermia, hypotension, hæmoconcentration, increased capillary permeability, hypochloræmia, depression of the nervous system; others are manifestations of active defence against shock, e.g. adrenal-cortical enlargement, increased corticotrophin and corticoid production, hyperchloræmia. If the causal stress is of medium intensity, the alarm reaction tends to evolve in two distinct phases, the phenomena of shock being followed by those of counter-shock. However, in most cases the manifestations of shock and defence are intermixed; indeed the sequence of events may even be reversed, e.g., in the case of progressively increasing fatal stress. Here

NOTES AND PREPARATIONS

NEW PREPARATIONS

ANACOBIN is a solution in normal saline of crystalline vitamin B₁₂, an erythropoietic principle of liver. Its use is indicated in the treatment of pernicious anemia in patients who have developed hypersensitivity to anahæmin or other refined liver extracts. Issued in ampoules of 10 microgrammes in 1 ml, in boxes of ampoules of 1 ml (British Drug Houses Ltd, Graham Street, London, N W 1)

ANALOS is a preparation free from sodium, and containing potassium chloride, ammonium chloride, potassium formate, calcium formate, and magnesium citrate. Its use is indicated in the salt-free diet prescribed for hypertension and obesity. Issued in sprinkler cartons of 56 g and 8 ounces (Antigen Laboratories Ltd, 95 Great Portland Street, London, W 1)

GIACURRANT COUGH LINCTUS, containing tincture of squill, tincture of scenega, syrup of tolu, syrup of wild cherry, glycerin, menthol, and 1/16 of a grain (4 mg) of eodine phosphate in each teaspoonful, is stated to be a stimulating expectorant and antiseptic with a sedative action and pleasant flavour. It is issued in bottles of 2½, 5 and 80 fluid ounces (Allen & Hanbury's Ltd, London, E C 2)

STREPTOMYCIN

A MINISTRY OF HEALTH notice states that as from November 1, 1949, streptomycin will be generally available on prescription. The toxic effects are stressed; they may be reduced by the substitution of dihydro-streptomycin, which, however, may manifest them on its own account. It is therefore important to employ adequate doses from the beginning of treatment and in certain conditions it may be preferable to give larger doses than usual for a period not exceeding one week, as serious toxic effects do not appear to develop within that period. In any case if the expected response is not obtained in that time, reconsideration of the treatment is indicated.

ROYAL MEDICAL BENEVOLENT FUND
LORD WEBB-JOHNSON, President of the Royal Benevolent Fund, writes:

"For the first time in the history of the Royal Medical Benevolent Fund the Chairman's Report is being sent to every member of the profession in England, Scotland and Wales. The Committee has felt justified in taking this step as the Fund is essentially the profession's own Benevolent Fund and all members of the profession should be informed of the useful and valuable work which is being done to alleviate the distress which exists within our own ranks. I ask all your readers to consider the Report as one of work to be continued by giving generously. Fund receives much help from many, but to those who are not subscribers I make this appeal. Please support your own Benevolent Fund by a subscription, large or small. Help to make the Fund worthy of our great and noble profession by having the personal support of every medical practitioner."

PUBLICATIONS

Special Breathing Exercises for Children is a charmingly produced pamphlet of breathing exercises for children which should induce any child to "have a try". It has been prepared by the Department of Child Health, Guy's Hospital, price 9d each, 33s for 50, 60s for 100, and £25 for 1000 copies post free.

Speech Therapists, in its seventh edition, contains the names of registered speech therapists qualified to treat disorders of speech. Copies can be obtained free on application to the Board of Registration of Medical Auxiliaries, British Medical Association House, Tavistock Square, London, W C 1.

Pharmaceutical Emulsions and Emulsifying Agents by L. M. Spilston, B. Pharm., M. P. S., in addition to chapters on the formation, properties, preparation and practical uses of emulsifying agents and emulsions, gives a classified list of over 300 emulsifying agents (Chemist & Druggist, 28 Essex Street, Strand, London, W C 2. Price 5s).

Twenty-eighth Report of the Home Ambulance Department of the Joint Committee of the Order of St. John and the British Red Cross Society deals with the subject of the ambulance service under the National Health Service Act, 1946 (12 Grosvenor Crescent, London, S W 1).

The Clinical Problems of Advancing Years. This beautifully produced symposium includes articles by well-known American physicians on such subjects as cardiovascular disease, obesity, drugs in geriatrics, chronic disease, and the general problems of advancing years. The publication celebrates the opening of the new factory and offices of the firm of Smith, Kline and French Laboratories, at 1530 Spring Garden Street, Philadelphia, U.S.A., and copies are available to practitioners on request.

PUBLISHERS' ANNOUNCEMENTS

The following pamphlets reprinted from material which originally appeared in THE PRACTITIONER are available exclusively to doctors for distribution to patients—

NOTES FOR THE PATIENT WITH INDIGESTION 12 pp

DIABETES FROM THE PATIENT'S POINT OF VIEW 8 pp

CONVALESCENCE AFTER HEAD INJURY (advice for the patient's relations) 8 pp

Price 6d each, or 10 for 4s 6d and 50 for £1 1s 6d, post free

IDIOTIC CASES IN WHICH LACTATION CAUSES PAIN IN THE CHEST 2 pp Price 1d each, postage extra

Erratum—In the article in the September issue on Protein Hydrolysis, by Professor John Beattie M.D., D.Sc., lines 13 and 18 on page 240 should read "The rate of infusion should not exceed 300 ml per hour."

The contents of a symposium page 1200 in at

h will contain be found on section

sclerosis, "rheumatic diseases", may represent by-products of the endocrine reactions which are at play in the general adaptation syndrome. These maladies are therefore believed to be "diseases of adaptation", that is, the results of excessive or abnormal adaptive reactions to stress (p. 398).

By "specific resistance" is meant that type of adjustment which increases resistance only against the particular type of stress to which the body has been exposed; conversely, "non-specific resistance" designates the ability of the body to withstand a type of stress qualitatively different from that to which it has become adapted. The term "adaptation energy" is used to describe the ability of the organism to acquire resistance to stress. By definition, any agent capable of producing an alarm reaction is an "alarming stimulus". Agents causing merely local damage, which requires no general adaptive adjustment, e.g. amputation of limbs, are relatively mild alarming stimuli, whilst those which evoke intensive adaptive responses, e.g. cold, solar or roentgen irradiation, muscular exercise, nervous stress, fasting, infections, intoxications, produce severe alarm-reaction symptoms. The alarm reaction is not necessarily a pathological phenomenon since it can be produced by mild exposure to stress, which is unavoidable in the course of everyday life.

THEORIES CONCERNING THE GENERAL ADAPTATION SYNDROME

The hypothesis of adaptation energy is based on the following observations: general resistance rises in the counter-shock phase of the alarm reaction, which intimates that the "adaptability" of the organism is "mobilized" in some manner. On the other hand, following prolonged exposure to stress, that is, during the resistant stage of the general adaptation syndrome, when the organism has acquired a high degree of adaptation to the agent to which it has been exposed, it becomes especially non-resistant and unable to adapt itself to other damaging stimuli. This suggested that the body may possess only a limited amount of adaptability or adaptation energy, which is consumed while adaptation is acquired to a certain agent, so that less of it remains available for resistance against other types of stress. Even continued treatment with the same agent, which originally caused an alarm reaction and to which the organism became adapted, eventually becomes damaging again ("stage of exhaustion" of the general adaptation syndrome). It would be extremely difficult to explain such a loss of acquired adaptation without assuming that due to continued "use" all the available adaptation energy of the organism had been exhausted.

To quote but one possible clinical application of this hypothesis, attention may be called to the fact that aviators who have to adapt themselves to work under nervous tension at high altitudes often break down following a period of apparently complete inurement. This breakdown is characterized, among other things, by gastro-intestinal disturbances and other manifestations reminiscent of the "stage of exhaustion" of the general adaptation syn-

some counter-shock develops first, when the body can still resist, but subsequently, shock manifestations become increasingly more prominent as the augmenting intensity of the stress makes further resistance impossible.

(2) *The stage of resistance* is defined as the sum of all non-specific systemic reactions caused by prolonged exposure to stimuli to which the organism has acquired adaptation. It is essentially a "protracted counter-shock". Resistance is increased to the particular agent to which the body has been exposed, and this is usually accompanied by a marked decrease in resistance to other types of stress. The impression is gained that during the stage of resistance, adaptation to one agent is acquired "at the expense of" resistance to other agents.

(3) *The stage of exhaustion* represents the sum of all non-specific systemic reactions which ultimately develop as the result of prolonged exposure to stimuli to which adaptation had been developed, but could no longer be maintained.

The three stages of the general adaptation syndrome are illustrated in the graph (fig. 1), based upon measurable variations in resistance to damage.

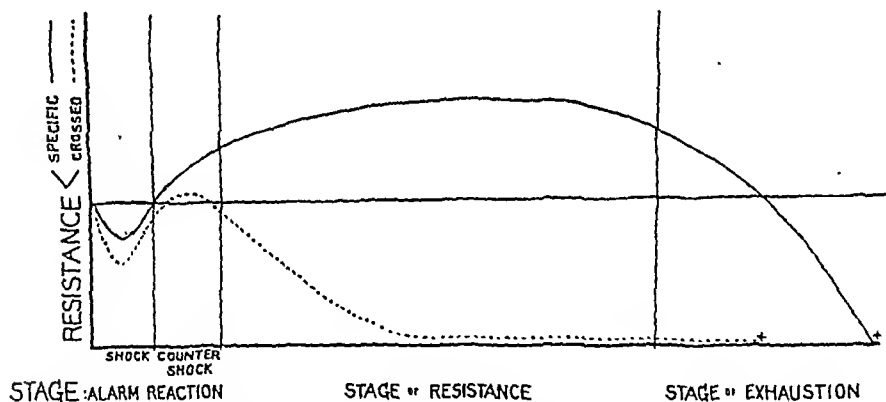


FIG. 1.—Schematic representation of the changes in specific (full line) and crossed (dotted line) resistance during the three stages of the general adaptation syndrome. The progress of time is indicated along the abscissa and the degree of resistance along the ordinate. Note that specific resistance to the agent with which the animal is treated decreases during the shock phase of the alarm reaction and increases during the counter-shock phase, reaching its maximum during the stage of resistance; in the stage of exhaustion, it falls below normal and finally, death ensues. Crossed resistance, to agents other than that with which pre-treatment occurred, falls even lower than the specific resistance during the shock phase, rises but slightly during the counter-shock phase, and is definitely subnormal in the stage of resistance. This indicates that whilst resistance to one agent (specific) is acquired by pre-treatment with this same agent, resistance to other stimuli (crossed resistance) falls below the normal level (horizontal line) (Selye, 1946).

It should be borne in mind, however, that many other manifestations of the syndrome develop concurrently in the same three-stage pattern.

Interest in the general adaptation syndrome has recently received a further impetus as a result of investigations suggesting that some of the most important diseases of clinical medicine, e.g. hypertension, nephro-

drome. In such cases it has been customary to speak of "exhaustion of the nervous energy reserve". The adaptation energy hypothesis cannot attempt to explain the pathogenic mechanisms responsible for the development of the adaptation syndrome. It is merely outlined as a working hypothesis which may help to visualize the fact that adaptation to a variety of stresses occurs in three distinct stages.

The functional, mainly hormonal, interrelations between the various organs affected by the general adaptation syndrome are much better understood (see fig. 2). It will be noted that "stress" initiates the entire chain of reactions. It appears to act upon the organism through two distinct pathways. The manifestations of damage (clinical "shock", loss of body weight and nitrogen, gastro-intestinal ulcers, transitory hyperkalæmia and hypochloræmia) are mediated through unidentified pathways (nervous stimuli(?), deficiencies(?), toxic metabolites(?), but certainly not through the hypophyseal-adrenal defence mechanism. They are not manifestations of defence, but rather of defencelessness. They are not prevented, but rather aggravated by hypophysectomy or adrenalectomy.

Secondly, again through unidentified pathways and perhaps through the above-mentioned blood-borne tissue catabolites, stress sets into action the hypophyseal-adrenal defence mechanism. It first acts upon the hypophysis, causing it to increase corticotrophin production at the expense of a decreased elaboration of gonadotrophins, luteotrophin and growth hormone. This leads to an inhibition of somatic growth, involution of the gonads and, if the reaction occurs during lactation, to cessation of milk secretion. It is this change in the type of pituitary hormones produced which is referred to as the "shift in hypophyseal hormone production".

The rise in corticotrophin secretion causes enlargement of the adrenal cortex with signs of increased *corticoid* production. These corticoids in turn produce changes in organic (gluco-corticoids) and inorganic (mineralo-corticoids) metabolism as well as atrophy of the thymus and other lymphatic tissues. At present, it is not quite clear whether corticoids destroy the circulating lymphocytes directly, or whether they influence the lymphocyte count merely by diminishing lymphocyte formation in lymphatic organs. Perhaps both these mechanisms are operative. It has been suggested, but not proven, that globulins, useful in the formation of antibodies, are produced during stress, due to the action of corticoids on the thymico-lymphatic apparatus, inasmuch as these globulins come from the bodies of disintegrating lymphocytes.

That stress actually affects the adrenal cortex through the hypophysis has been proven in experiments on hypophysectomized animals, in which stress has no effect either upon the adrenal cortex or upon any other organ indicated on the graph (fig. 2), below the level of the hypophysis; correspondingly, adrenalectomy prevents the effect of either stress or hypophyseal extracts upon the organs shown below the level of the adrenal; administration of corticoids can affect these terminal target organs directly, irres-

causes hypertrophy of the cells in these segments and hypertension, long before there is any nephrosclerosis. Later, however, when the sclerosis of the renal vessels becomes manifest, there arises a vicious circle inasmuch as nephrosclerosis aggravates hypertension and hypertension increases nephrosclerosis.

Recent observations suggest that the tubular damage caused by mineralo-corticoids can interfere with the normal inactivation of renal pressor substances. Furthermore, the regulation of the blood volume by the kidney can be deranged by overdosage with these corticoids, especially if the sodium intake is high. Which of these factors plays the major part in the causation of hypertensive diseases appears to depend largely upon experimental conditions.

Presumably, the increased *blood pressure* (perhaps in conjunction with direct toxic actions of sodium and/or renal pressor substances) causes changes in *the heart* (infarcts, Aschoff(?) nodules) and the blood vessels (periarteritis nodosa) (fig. 3).

We have no explanation for the production of *joint lesions* (polyarthritis) which is occasionally seen under the influence of mineralo-corticoids or impure pituitary extracts. It is probable, however, that the beneficial effect of gluco-corticoids and corticotrophin upon rheumatoid arthritis is somehow related to this arthrotropic action of corticoids.

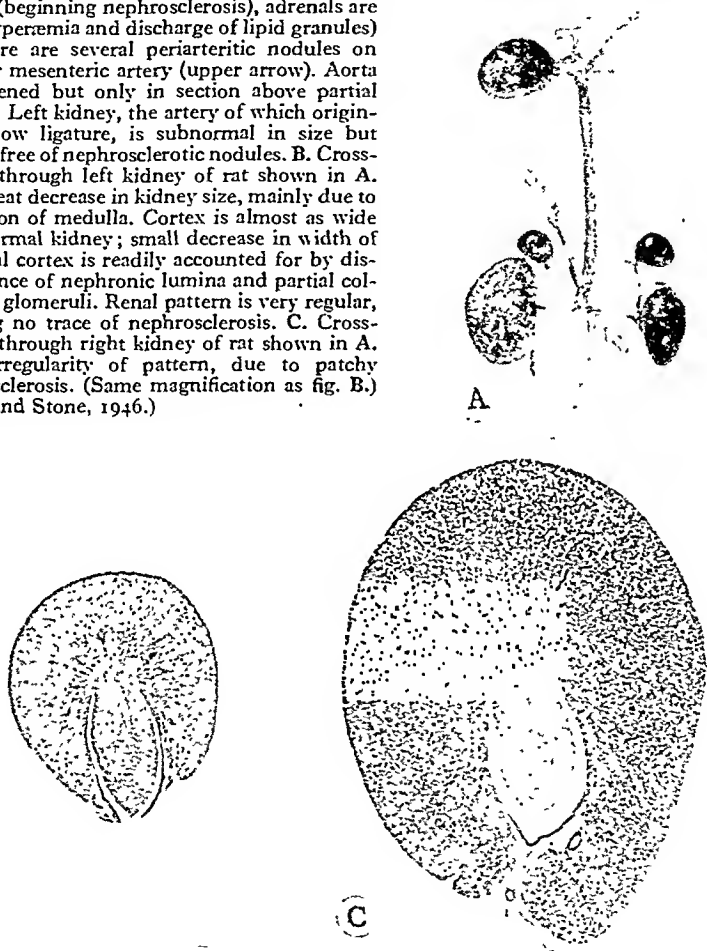
CLINICAL IMPLICATIONS OF THE GENERAL ADAPTATION SYNDROME

Adaptation to our surroundings is one of the most important physiological reactions in life; one might perhaps even go so far as to say that the capacity of adjustment to external stimuli is the most characteristic feature of living matter. It is not unexpected therefore that some of the most common diseases of man appear to be diseases of the adaptive mechanism. There is increasingly more evidence to show that the diseases of adaptation play the same important rôle in pathology as the general adaptation syndrome in physiology. The maladies which should be considered as possibly belonging to the group of the "diseases of adaptation" are the following:—

Hypertension and "hypertensive diseases".—Since under certain conditions hypertension can be produced experimentally in animals by continued exposure to stress, it is reasonable to assume that spontaneous hypertensive disease in man may also occur as a result of chronic exposure to non-specific damaging agents. In such cases it is likely that stress causes an increased corticotrophin production by the anterior lobe, and this in turn stimulates the corticoid hormone production of the adrenals; the resulting hypertension and nephrosclerosis could then be due to an endogenous intoxication with the organism's own corticoids. Not every kind of damage is equally prone to raise the blood pressure through this mechanism. Various types of stress lead to different degrees of corticoid hormone over-production, and perhaps some stimulate gluco-corticoid rather than mineralo-

corticoid secretion; only the latter causing nephrosclerosis with hypertension. Furthermore, hypertension would not result if the metabolic changes caused by the stress created unfavourable conditions for the development of corticoid intoxication. The observation that diets poor in

FIG. 3.—The endocrine kidney. A. Macroscopic view of heart, aorta, kidney and adrenals of a rat. The aorta was partially ligated between origin of 2 renal arteries (lower arrow), and lyophilized anterior pituitary (LAP) treatment was given during 14 days. Note enlargement of heart, adrenals and right kidney. Heart contained macroscopically visible Aschoff (?) nodules, kidney surface is irregular (beginning nephrosclerosis), adrenals are dark (hyperemia and discharge of lipid granules) and there are several periarteritic nodules on superior mesenteric artery (upper arrow). Aorta is thickened but only in section above partial ligature. Left kidney, the artery of which originates below ligature, is subnormal in size but entirely free of nephrosclerotic nodules. B. Cross-section through left kidney of rat shown in A. Note great decrease in kidney size, mainly due to involution of medulla. Cortex is almost as wide as in normal kidney; small decrease in width of the renal cortex is readily accounted for by disappearance of nephronic lumina and partial collapse of glomeruli. Renal pattern is very regular, showing no trace of nephrosclerosis. C. Cross-section through right kidney of rat shown in A. Note irregularity of pattern, due to patchy nephrosclerosis. (Same magnification as fig. B.) (Selye and Stone, 1946.)



sodium and protein or the production of acidosis (through the administration of NH_4Cl or other acidifying salts) counteract the toxicity of corticotrophins, clearly indicates that the damaging action of the latter is conditional upon the state of metabolism as a whole.

Periarteritis nodosa.—In animals chronically treated with desoxycorti-

costerone, and in sensitized (unilaterally nephrectomized, high-sodium and high-protein diet) animals exposed to certain types of stress, e.g. cold, diffuse periarteritis nodosa develops, especially in the mesenteric, cardiac and brain vessels. Histologically, this periarteritis nodosa is so similar to

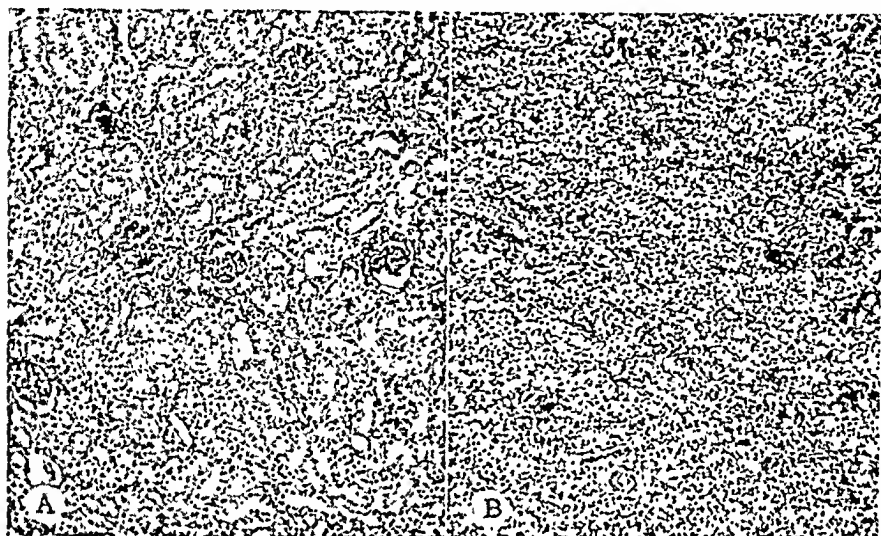


FIG. 4.—The endocrine kidney. A. High magnification of an area from normal control kidney. B. High magnification of an area from left "endocrine kidney" of a rat whose aorta was partially ligated between origins of two renal arteries. Note that all tubular lumina and Bowman's capsule spaces have disappeared. Glomeruli tend to melt in with tubular parenchyma but are still distinguishable in places (2 arrows). A small arteriole, near lower margin (1 arrow) shows no trace of hyalinization. General pattern of this kidney is reminiscent of an adrenal or parathyroid, since it consists exclusively of solid, epithelial cell cords. (Same magnification as A.) (Selye and Stone, 1946.)

the intrarenal vascular lesions of malignant nephrosclerosis that it is tempting to assume that nephrosclerosis and periarteritis nodosa are both results of the same pathogenic mechanism (fig. 6).

Spontaneous periarteritis nodosa is often seen in man as a sequel of acute rheumatic fever. It has even been considered to be a type of "rheumatic arteritis", and exhibits the same histological characteristics and the same distribution in the various vascular territories as the experimental form produced by corticoids. It is probable therefore that periarteritis nodosa likewise belongs to the diseases of adaptation caused by abnormal adrenal-cortical hyperactivity. It is doubtful whether *arteriosclerosis* merely represents a particularly chronic form of essentially the same vascular lesions as are found in periarteritis nodosa. Since *arteriosclerosis* also tends to occur in individuals exposed to continuous stress and is likewise accompanied by hypertension, there may be some relationship between these two types of vascular lesions.

Nephrosclerosis.—The facts mentioned above in connexion with hypertension are equally applicable to nephrosclerosis, hence they need not be

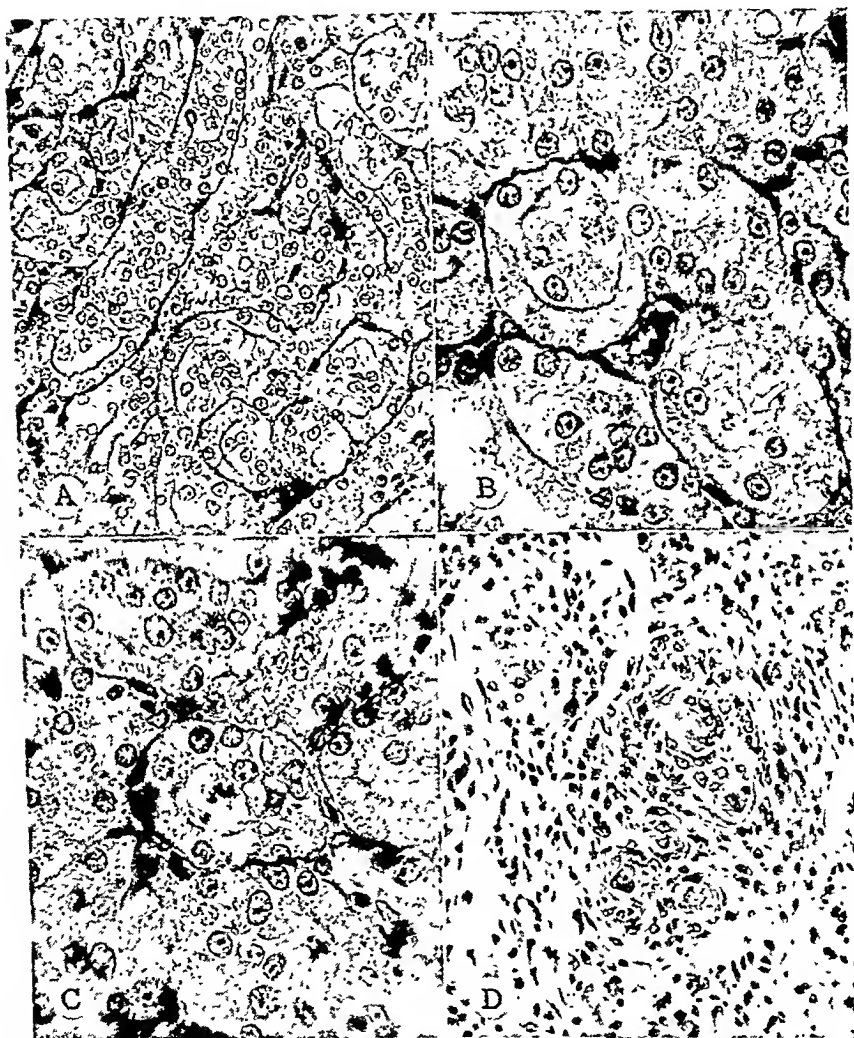


FIG. 5.—The endocrine kidney. A. High magnification of an area from left “endocrine kidney” of an LAP-treated rat whose aorta was partially ligated between the two renal arteries. Note solid epithelial parenchyma, although no secretion of urine occurs and tubular lumina are absent, epithelial cells are well preserved and show no sign of degeneration or necrosis. B. Another field of same kidney under oil immersion. Note that tubular lumina are filled with proliferating epithelial cells. A mitotic figure (arrow) is seen in a convoluted tubule. Note also syncytial formation near upper and lower right-hand corner and rather polymorph appearance of nuclei. C. Another area of the kidney shown in A. Polymorph appearance of nuclei and a large mitotic figure in centre of field (arrow) are clearly visible. Many mitotic divisions in these kidneys clearly indicate that renotropic stimulation is possible even in small “endocrine kidney”. D. Section through a myocardial nodule of another rat treated with LAP. Note proliferation of capillary endothelium which tends to fuse and thus form polynuclear giant cells similar to those seen in acute rheumatic fever; myocardial fibres have been completely replaced by granulomatous tissue. (Selye and Stone, 1946.)

repeated here. It is evident that under the influence of the vascular lesions produced by corticoids, the lumina of the renal arterioles are greatly reduced; this decreases the blood pressure in the kidney, a change known to cause an increased production of pressor substance (probably renin). Thus a vicious circle results: the more the blood pressure rises, the more the lumina of the renal arterioles shrink due to the blood-vessel-damaging effect of high blood pressure; correspondingly, the kidney continues to increase its pressor-hormone production.

In this connexion it is noteworthy that constriction of the renal artery, by means of an intervention which permits a decrease in the intra-glomerular pressure to the level of the protein-osmotic pressure of the blood, abolishes

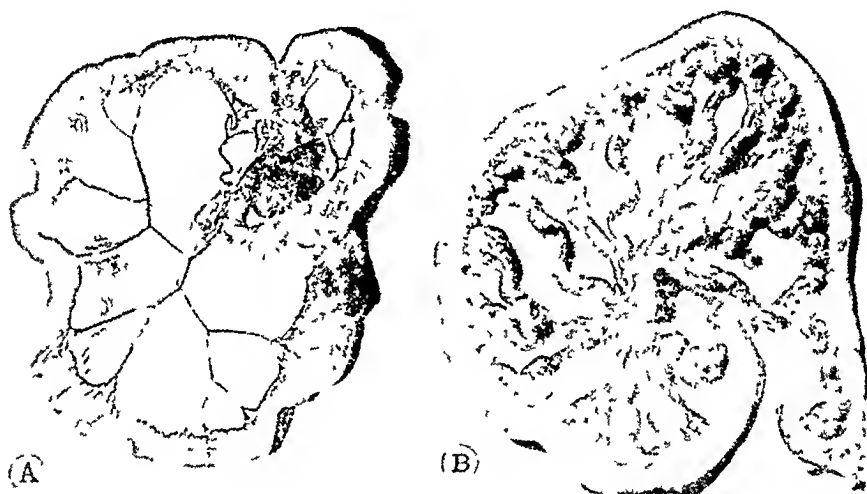


FIG 6—*Periarthritis nodosa* caused by the "endocrine kidney". A. A loop of small intestine in a normal control rat (body weight 120 g) showing the normal aspect of the mesenteric vessels. B. Pronounced thickening of all mesenteric vessels which showed the histological characteristics of *periarthritis nodosa*. In this rat (body weight 125 g) a partially constricting ligature had been placed, 38 days previously, on the aorta between the origins of the two renal arteries. It caused complete endocrine transformation of the left kidney, accompanied by marked hypertensive disease.

urine secretion by eliminating the filtration pressure; consequently the entire kidney is transformed into purely endocrine tissue. Thus, we obtain an exclusively "endocrine kidney" which does not participate in urine formation (fig 4, 5). This morphological transformation of one kidney is accompanied by the most acute and malignant type of nephrosclerosis in the contralateral kidney and by severe, usually fatal, hypertension. Significantly, no nephrosclerosis occurs in the kidney in which the blood pressure has been decreased, this suggests that nephrosclerosis is largely dependent upon the increase in blood pressure and is not solely caused by humoral factors. Since both the endocrine and the other kidney of such

test animals are perfused with the same blood, the nephrosclerosis, were it due to purely chemical stimuli, should be equal on both sides. It is probable that, both in spontaneous and in experimental nephrosclerosis, hyalinization of certain glomeruli transforms individual nephrons into "endocrine nephrons", since such hyalinization has approximately the same effect upon the individual nephron as the operation for the production of the "endocrine kidney" has upon the entire organ. However, mineralo-corticoids undoubtedly also possess a direct stimulating action upon the cells of the spiral segments. During desoxycorticosterone treatment, for instance, these parts of the tubules enlarge as soon as the blood pressure rises; long before there is any trace of an organic vessel lesion.

Nephritis.—In very acute corticoid or corticotrophin intoxication, actual inflammatory lesions have been seen in the kidney; the possibility must be considered that nephritis may be an especially acute type of the same change which causes nephrosclerosis. The frequent occurrence of nephritis during the recovery period from acute infectious diseases, e.g. scarlet fever, diphtheria, raises the possibility that the disease may be due to excessive corticoid production at a time when the defence mechanism against the infection has fully developed.

Rheumatic diseases.—Granulomatous nodules (similar to Aschoff nodules), endocardial vegetations, pericardial transudates, and sometimes even acute joint lesions tend to occur in animals receiving excessive amounts of mineralo-corticoids. This suggested that the so-called cryptogenic rheumatic diseases may likewise represent diseases of adaptation due to endogenous corticoid intoxication. It is known that fatigue, chills, traumatic injuries, or mental upset, may cause the relapse of a patient with rheumatic fever from a quiescent into an acute febrile state. Here again, the main problem is to find a common pathway which could explain the similarity of the lesions produced by such a variety of agents. Acceptance of the hypophyseo-adrenal theory does not necessitate abandonment of other interpretations. It merely implies that such agents as cold, micro-organisms, or serologic disturbances, can so influence the hypophyseo-adrenal defence mechanism that an excessive amount of mineralo-corticoid hormone is elaborated whenever an individual is exposed to them; the rheumatic attack would then result from such a derailed defence mechanism.

CONCLUSIONS

Much further work is required to elucidate the complexities of the diseases of adaptation. In the foregoing paragraphs I have only attempted to give a general outline of this problem, since it is potentially of great importance, not only for endocrinology, but for medicine as a whole. If the concept of the "diseases of adaptation" should prove to be correct, it must be concluded that endocrine derangements play a decisive part in the major, fatal syndromes of internal medicine.

At first, it is difficult to understand why a single mechanism, namely, increased corticoid hormone production, should lead to such a variety of apparently unrelated diseases. Hereditary predisposition, a *locus minoris resistantiae* in one or the other target organ, or the diet, are all likely to influence the response of the various organ systems in any particular individual. Even in experimental animals treated with pure desoxycorticosterone, renal lesions will be prominent in one case, heart lesions in another, and so on. At the time when the etiology of tuberculosis was not known, it appeared very improbable that a single micro-organism could produce so seemingly diverse diseases as Pott's disease of the bones, tuberculosis of the lungs, and lupus of the skin. Yet, it is now a generally accepted fact that all these maladies are due to the tubercle bacillus.

It may be argued further, that nature is not likely to provide a defensive mechanism which eventually defeats its own purpose. Yet, serum sickness and anaphylactic reactions are excellent examples of essentially useful defensive phenomena which can "de-rail" and then cause death. Even in endocrinology similar instances can be mentioned. Renal rickets is a bone lesion caused by excess parathyroid hormone secretion in children with severe renal disease. In these, the insufficiency of the kidney causes hyperphosphatemia and other metabolic disturbances, which are combated by a compensatory increase in parathyroid hormone secretion to maintain life. However, the secondary consequences of this defensive hyperparathyroidism are detrimental, since they produce bone resorption and skeletal deformity.

The most important objection to our concept appears to be that continued exposure to stress (chronic infections, endogenous intoxications), does not regularly produce "diseases of adaptation". However, as already stated, the latter diseases are not part of the general adaptation syndrome to stress, but represent derailments of the latter during the phase of resistance. Apparently, under normal conditions, increased corticotrophin production is accompanied by such metabolic changes as prevent the toxicity of the hormone, just as low-protein, low-sodium diets or acidifying salts prevent them. The diseases of adaptation can therefore only ensue if metabolic conditions are favourable for the manifestation of hypercorticism.

The recent reports of Hench and his colleagues (1949) from the Mayo Clinic, indicating that rheumatoid lesions and perhaps even rheumatic fever show a truly dramatic improvement upon treatment with cortisone or ACTH, are of paramount importance. The almost simultaneous report of Perera and Pines (1949) that the hypertension which can be elicited with desoxycorticosterone in man is abolished by an adrenal extract containing gluco-corticoids, is probably of equal importance. These findings appear to support the seemingly far-fetched view that the adrenal cortex plays a part in the pathogenesis of the above-mentioned diseases; at the same time they give us hope that a better understanding of the general adaptation

syndrome may furnish us with a useful new approach to the therapy of various diseases.

The following preliminary classification may help to survey the possible clinical implications of the general adaptation syndrome theory:—

DISEASES OF ADAPTATION DUE TO ENDOCRINE DISTURBANCES

(1) HYPERFUNCTIONAL:

(a) *Primary diseases of endocrines which participate in the general adaptation syndrome*

- (1) Cushing's disease (pituitary hyperfunction).
- (2) Adrenal tumours with "Cushing's syndrome" (adrenal-cortical hyperfunction).
- (3) Chromaffinomas (adrenal-medullary hyperfunction).
- (4) Coarctation of the renal artery and other primary diseases of the kidney conducive to hypertension (renal hyperfunction [hormonal]).

(b) *Secondary diseases due to excessive (or abnormal) response of endocrines to stress*

- (1) Some types of hypertension.
- (2) Periarteritis nodosa (also arteriosclerosis and other vascular lesions?).
- (3) Nephrosclerosis.
- (4) Some types of nephritis (?).
- (5) Rheumatic diseases (?).
- (6) Waterhouse-Friedrichsen syndrome.
- (7) Eclampsia (?).
- (8) Accidental thymus-involution.
- (9) Some types of appendicitis (?).
- (10) Some types of tonsillitis (?).
- (11) Gouty arthritis (?).
- (12) Some types of diabetes.

(2) HYPOFUNCTIONAL:

(a) *Primary diseases of endocrines which participate in the general adaptation syndrome*

- (1) Simmonds's disease (pituitary hypofunction).
- (2) Addison's disease ("status thymico-lymphaticus" (?); adrenal-cortical hypofunction).

(b) *Secondary diseases due to insufficient response of endocrines to stress*

- (1) Secondary shock (relative hypocorticism (?)).
- (2) Acute gastro-intestinal erosions ("Curling's ulcer").

References

- Hench, P. S., *et al.* (1949): *Proc. Mayo Clin.*, 24, 181, 277.
 Perera, G. A., and Pines, K. L. (1949): *Proc. Soc. exp. Biol. N.Y.*, 71, 443.
 Selye, H. (1946): *J. clin. Endocrinol.*, 6, 117.
 —, and Stone, H. (1946): *J. Urol.*, 56, 399.

This article is based upon a chapter in my forthcoming book "Textbook of Endocrinology" (Acta Endocrinologica Inc. Publ., Montreal, Canada).

THE PROBLEM OF THE ETIOLOGY OF THYROTOXICOSIS

By F. T. G. PRUNTY, M.D., M.R.C.P.

*Reader in Chemical Pathology, University of London; Physician,
St. Thomas's Hospital.*

THAT the occurrence of simple goitre may be an endemic phenomenon has been recognized at least since the time of Pliny, who correlated its existence with abnormalities of the water supply. The recognition of thyrotoxicosis was not achieved until its description by Parry in 1825. Before considering the question of the etiology of thyrotoxicosis, some consideration must first be given to that of simple goitre. There is extensive and detailed documentation of factors associated with its development, and perhaps the most impressive of these is its geographical distribution. Whilst in general the occurrence of the enlarged thyroid is widespread in mountainous districts removed from the sea, it also occurs in lower lying districts, around the Great Lakes of N. America, for example, and in island communities such as New Zealand and Great Britain. In these locations and in Switzerland reliable data are available correlating the goitre incidence with lack of iodine in water and soil, and it is undisputed that such deficiency is one of the primary causes of the condition (M.R.C. Memorandum, 1948).

Recently, additional observations have revealed that there exist naturally occurring "goitrogens", containing antithyroid substances, and of these the cabbage and members of the brassica family are of greatest importance. Rape seed and soya bean have also been incriminated. Thus the appearance of "outbreaks" of goitre in Belgium during the recent war has been linked with increased consumption of brassica vegetables (Bastenie, 1947), and this may be true in other areas where it is difficult to demonstrate a clear-cut iodine deficiency.

The natural behaviour of simple goitre has been the subject of study in both humans and dogs (Marine, 1924). Epithelial hyperplasia in either normal glands or in colloid goitres readily occurs when iodine intake is very restricted, and is reversed by its administration. The subsidence of such hyperplasia in a previously normal gland when small amounts of iodine become available may be accompanied by the formation of colloid vesicles. In this way a colloid goitre results which itself may undergo cycles of hyperplasia and involution. What relation may thyrotoxicosis bear to such a cycle of events? This condition is characteristically accompanied by hyperplastic epithelium functioning at a greater rate than normal. This hyperplasia may be generalized in the gland, in which case there is a clinical uniform soft enlargement of the gland, or it may be part of a "nodular" thyroid. The formation of nodules in endemic goitres is a feature of human

thyroids and not of those in animals, and it tends to increase with advancing age. Some nodules are "adenomatous" in nature, consisting of potentially functional epithelium, and show gradations from so-called "fœtal adenoma" to differentiated hyperplastic tissue.

This nodular thyroid is found often with the type of thyrotoxicosis associated with the name of Plummer, and later known as "secondary thyrotoxicosis". It was differentiated from Graves's disease on account of its somewhat different symptomatology, which is too well known to need description. By the use of the radio-autographic technique using radioactive I^{131} , it can be shown that such toxic nodular goitres have increased function in the "adenomatous" nodule or in the intervening hyperplastic tissue. If the sum of the activities of these two sources becomes too great, toxicity results. There is much evidence, especially in the older literature, to show that the administration of excessive iodine may cause exacerbation of Graves's disease and, still more important, induce thyrotoxicosis in patients with simple goitre. This type of toxicity is referred to on the Continent as Iod-Basedow, to distinguish it from spontaneous Basedow's disease (thyrotoxicosis). If this condition is a reality it can be regarded as one possible mechanism in the link between simple goitre and thyrotoxicosis.

OCCURRENCE OF THYROTOXICOSIS

Endemicity.—Thyrotoxicosis is a condition which is worldwide in distribution, but apparently follows no very close geographical correlation with the occurrence of simple goitre. However, from a study of the thyrotoxicosis death rate in England, the distribution largely overlaps that of endemic goitre in schoolchildren, being maximal in the western parts of the country and in Wales (Campbell, 1924). The reason for this endemicity is not clear, but consumption of goitrogenic substances may play some part. On the other hand, in N. America the severity of thyrotoxicosis appears to be no greater in an endemic goitrous area (Chicago) than in a non-endemic area (Massachusetts) (Means, 1948). Nevertheless, the view is often held that a nodular goitre is very likely to become toxic sooner or later. Thyrotoxicosis occurs throughout the life span of the human but is most frequent during the second to fourth decades, and the incidence in the female sex is particularly high. The time of appearance of simple goitre is also of considerable importance.

Menstruation and pregnancy.—In severe endemic areas all members of the population are likely to be affected, but in less severe areas the goitre incidence becomes greatest in females, particularly at and after puberty. In this connexion the widespread occurrence of puberty goitre in girls in non-endemic areas is worthy of note, and is often considered to be almost physiological. It is possible to detect rhythmic thyroïdal enlargement in women in connexion with the menses. Pregnancy too, has been associated with increase in size of simple goitres in endemic areas, and the offspring of these mothers have a greater chance of developing goitres than had their

parents. The relationship of pregnancy to thyrotoxicosis has been carefully studied (Gardiner-Hill, 1929). Nearly half the cases of thyrotoxicosis in women during the child-bearing period developed during or immediately after pregnancy, indicating an increased susceptibility at this time.

The part played by *heredity* in thyrotoxicosis is more difficult to assess. It occurs in identical twins and the incidence suggests that it is transmitted by a recessive factor concerned with a predisposition to a thyrotoxic diathesis. Certain cases are undoubtedly associated with a family history of the condition, but it is likely that the genes concerned have a low incidence of expression. In the case of endemic goitre there is no doubt that the severity of the condition increases in successive generations and inter-marriage is, of course, often frequent in endemic localities. On removal of a goitrous family from an endemic area the goitrous tendency rapidly disappears in the course of one or two generations.

The existence of certain *extrinsic precipitating factors* concerned with the onset of thyrotoxicosis is widely claimed. The chief among these are anxiety, worry, mental shock and infections. During the recent war the number of cases in which the onset of the condition dated from a "bomb incident" appeared to be noticeable, and frequently the patients became bereaved on these occasions. Nevertheless, it is difficult to determine if in fact there was an etiological relationship between the two events, especially during periods when the bombing incidence was widespread. It has been observed that thyrotoxicosis was almost unknown in the British Army during the two wars or in the United States Army during the recent war (*Lancet*, 1947; Means, 1948). The incidence in the civilian population remained high. Apparently local causes of unknown type may suddenly operate in the precipitation of a toxic state. Meulengracht (1945) described a sudden marked increase of incidence in Copenhagen during the German occupation, and Plummer (1928) reported a similar outbreak of thyrotoxicosis in the mid-western parts of the United States in the middle and late 1920's.

Stress has hitherto been placed on the importance of *infections* in the genesis of a toxic state, and the most important are said to be tonsillitis and influenza (Gardiner-Hill, 1929). However, it must be pointed out that thyrotoxicosis is only one of many conditions which has been related to focal sepsis, and that, after search, sepsis in the hospital patient is by no means an infrequent finding.

FUNCTIONAL ALTERATIONS IN THE THYROID GLAND

The relation to the anterior pituitary.—The thyroid gland is subject to stimulation by the thyrotrophic hormone of the anterior pituitary (TSH), which produces in a resting gland increase of the height of the epithelial cells lining the acini. This hypertrophy is shortly followed by hyperplasia and increase in the weight of the gland, if the amount of TSH is sufficient. Meanwhile there is stimulation of release of thyroid hormone, which is believed to be achieved by proteolytic degradation of the colloidal thyro-

globulin, with the transfer of its products through the cells to the circulation. Subsequently there is increased production of thyroxine with increased uptake by the gland of inorganic iodine. These findings have been facilitated by the use of tracer amounts of I^{131} .

The problem of the fate of pituitary trophic hormones after stimulation of the target gland is of great importance, and in the case of TSH has been the subject of fruitful study. Incubation of thyroid tissue with TSH leads to the disappearance of the activity of the TSH, and this can be reactivated by reducing agents (Rawson, 1948a). Most important is the finding that tissue from thyrotoxic glands has the capacity of inactivating larger amounts of TSH. The action of TSH on the thyroid epithelium appears to be inhibited by inorganic iodine, which suppresses the secretion of thyroxine. TSH also has the property of eliciting the formation of an antithyrotrophin in the blood of animals injected with the hormone, but the inhibitory effect of the anti-TSH may be overcome by the injection of doses of TSH of increased amount (Loeser, 1937). TSH is protein in nature, and the question whether the antithyrotrophic response is to the injected protein or is a true "anti-hormone" remains unsettled. Endogenous secretion of TSH is suppressed by thyroxine, so that the output of TSH is partly regulated by the amount of circulating thyroxine. Its secretion is also controlled by stimuli from the hypothalamic region to the anterior pituitary. It is possible that such stimulation may be effected in part by a hormonal mechanism, by way of the portal system of vessels from the neighbourhood of the tuber cinereum to the anterior pituitary described by Harris (1948). Hence there exists a possible pathway for the transmission of stimuli causing mental trauma or anxiety to the anterior pituitary. It is believed that the nerve supply to the thyroid itself is concerned only with vascular innervation, but this in itself may be of importance in so far as increased blood supply to the gland may be induced by such a mechanism.

Some insight into the rôle of TSH in the induction of thyrotoxicosis has been sought from reference to the occurrence and behaviour of exophthalmos and ophthalmoplegia. It is well known that exophthalmos can be produced in animals by the injection of TSH, either in the presence or absence of the thyroid gland. There is, however, controversy concerning the nature of this exophthalmos. Analysis (Rundle and Pochin, 1944; Pochin, 1945) suggests that in Graves's disease the orbital contents undergo fatty infiltration, whereas experimental exophthalmos is mainly due to oedema of the orbital tissues. This difference may be more quantitative than fundamental in nature, and needs further investigation. It is widely assumed that clinical exophthalmic ophthalmoplegia bears some relation to TSH activity. It commonly occurs in patients who are not markedly thyrotoxic, and often arises as a result of thyroidectomy in toxic individuals. Furthermore, it is rare in patients with toxic nodular goitres, and Means is of the opinion that there are two types of thyrotoxicosis, one of these being the ophthalmopathic form. If one accepts for the moment that the eye lesion indicates increase of

TSH activity, one is left with the difficulty of explaining how it is that the thyroid does not react with increased activity and the production of thyrotoxicosis. If the process of inactivation of TSH by the thyroid epithelium plays a fundamental part in the activity of the gland this might be understood. It could be the case that the inactivation of TSH was intimately concerned with excess epithelial function in the gland, producing thyrotoxicosis and inactivating TSH, so far as the orbit was concerned. Thus might arise thyrotoxicosis in the absence of the eye lesion. On the other hand, if the thyroid was somewhat refractory in its inactivation of TSH there would be a tendency for excessive secretion of TSH, failing to produce thyrotoxicosis but causing exophthalmos. It is also possible that failure of thyroid response to TSH may be due to the presence of increased antithyrotrophin which prevents the action of TSH on the thyroid but not on the orbital contents, but this seems doubtful (Pochin, 1945), although the possibility has been discussed by Brain (1948).

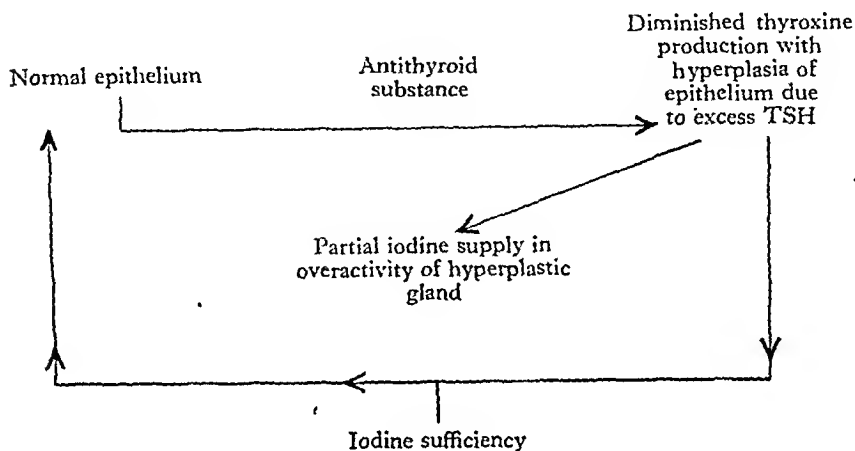
Many attempts have been made to demonstrate increased production of TSH in thyrotoxicosis, with somewhat unconvincing results, by attempting the assay of TSH in urine in thyrotoxicosis and myxoedema. Using a more recently developed and more sensitive method a group of hyperthyroid patients with ocular manifestations have been observed to have high levels of blood TSH, lowered in one instance by thyroid administration (de Robertis, 1948). This author, too, considers that there may be two types of Graves's disease. However, if Rawson's observations of increased inactivation of TSH by hyperthyroid tissue are substantiated, it might be expected to be doubtful whether searching for evidence of increased circulating TSH is likely to yield positive results. This question awaits further investigation.

INHIBITION OF THYROXINE

Study of the action of antithyroid drugs has produced much information which will throw some light on the way in which thyrotoxicosis occurs. These drugs are in general goitrogenic, leading to epithelial hyperplasia. This is true of both thiocyanates, thiocyanate goitre being a well-recognized complication of the use of the drug in the treatment of hypertension, and of thiourea and thiouracil derivatives. In addition, these drugs all suppress thyroid activity, in the sense that the secretion of thyroxine is diminished, either by suppressing the uptake of inorganic iodide or by interfering with the oxidation of the iodine prior to its utilization in the formation of the organic iodine derivatives. Thus thyroxine formation is inhibited, and in turn permits greater secretion of TSH by the anterior pituitary. In this way there results a tendency to hyperplasia of the epithelium which is inhibited by iodine administration, in the same way that hyperplasia in thyrotoxicosis can be reversed. Iodine appears also to have some controlling influence on the formation of organic iodine compounds in the gland, for high blood levels of iodine in the chick permit the gland to take up inorganic iodine, but prevent its utilization in the formation of thyroxine (Wolff and Chaikoff,

1948). Recent studies on iodine metabolism lend no support to the older concept that a state of "dysthyroidism" is of importance in the production of toxicity. It was supposed that there was a type of thyroid diarrhœa of a partially iodinated and toxic thyroglobulin.

Just as Marine has postulated a cycle of hyperplasia and involution in the production of goitres, so it may be possible that a functional cycle can occur in the thyroid mechanism. This could be disturbed, with the production of thyrotoxicosis:—



RELATION TO OTHER ENDOCRINE GLANDS

Much work needs to be done upon the question of the relation of the thyroid to other glands in the body. The striking etiological correlation of sex and the sexual phases with thyrotoxicosis indicates a special rôle of the female sex hormones. There is general evidence of pituitary inhibition by œstrogens and slight indications that these substances reduce the thyrotoxic state in menopausal patients, but this is still in the preliminary stage of investigation. The importance of the adrenal, both cortex and medulla, has also been considered. Present knowledge suggests that adrenal cortical changes are of a secondary nature and that there can be a tendency for the cortical secretion to lag behind the demands made by the hyperthyroid state.

FUNCTIONING NEOPLASMS

Finally, the question of functioning neoplasms of the thyroid must be considered. A few differentiated carcinomas of the thyroid produce a toxic state, and the uptake of iodine by neoplasms has been stimulated with TSH. The hormone production of such neoplasms is not inhibited by thiouracil (Rawson, 1948b) and the increased function appears to be an intrinsic property of the neoplastic tissue. This behaviour again raises the question as to how far it is justifiable to regard some of the "adenomas"

TSH activity, one is left with the difficulty of explaining how it is that the thyroid does not react with increased activity and the production of thyrotoxicosis. If the process of inactivation of TSH by the thyroid epithelium plays a fundamental part in the activity of the gland this might be understood. It could be the case that the inactivation of TSH was intimately concerned with excess epithelial function in the gland, producing thyrotoxicosis and inactivating TSH, so far as the orbit was concerned. Thus might arise thyrotoxicosis in the absence of the eye lesion. On the other hand, if the thyroid was somewhat refractory in its inactivation of TSH there would be a tendency for excessive secretion of TSH, failing to produce thyrotoxicosis but causing exophthalmos. It is also possible that failure of thyroid response to TSH may be due to the presence of increased antithyrotrophin which prevents the action of TSH on the thyroid but not on the orbital contents, but this seems doubtful (Pochin, 1945), although the possibility has been discussed by Brain (1948).

Many attempts have been made to demonstrate increased production of TSH in thyrotoxicosis, with somewhat unconvincing results, by attempting the assay of TSH in urine in thyrotoxicosis and myxœdema. Using a more recently developed and more sensitive method a group of hyperthyroid patients with ocular manifestations have been observed to have high levels of blood TSH, lowered in one instance by thyroid administration (de Robertis, 1948). This author, too, considers that there may be two types of Graves's disease. However, if Rawson's observations of increased inactivation of TSH by hyperthyroid tissue are substantiated, it might be expected to be doubtful whether searching for evidence of increased circulating TSH is likely to yield positive results. This question awaits further investigation.

INHIBITION OF THYROXINE

Study of the action of antithyroid drugs has produced much information which will throw some light on the way in which thyrotoxicosis occurs. These drugs are in general goitrogenic, leading to epithelial hyperplasia. This is true of both thiocyanates, thiocyanate goitre being a well-recognized complication of the use of the drug in the treatment of hypertension, and of thiourea and thiouracil derivatives. In addition, these drugs all suppress thyroid activity, in the sense that the secretion of thyroxine is diminished, either by suppressing the uptake of inorganic iodide or by interfering with the oxidation of the iodine prior to its utilization in the formation of the organic iodine derivatives. Thus thyroxine formation is inhibited, and in turn permits greater secretion of TSH by the anterior pituitary. In this way there results a tendency to hyperplasia of the epithelium which is inhibited by iodine administration, in the same way that hyperplasia in thyrotoxicosis can be reversed. Iodine appears also to have some controlling influence on the formation of organic iodine compounds in the gland, for high blood levels of iodine in the chick permit the gland to take up inorganic iodine, but prevent its utilization in the formation of thyroxine (Wolff and Chaikoff,

THE TREATMENT OF DIABETES MELLITUS IN INFANCY AND CHILDHOOD

By HERMON WHITTAKER, M.R.C.P.

Consultant to the Hostels for Diabetic Children of the London County Council and the Children's Society; Physician, Diabetic Clinic, Queen Mary's Hospital for the East End; First Assistant, Diabetic Department, King's College Hospital.

ALTHOUGH diabetes mellitus is rare in infants, Henderson's survey (1949) gave the numbers of diabetic children of school age in this country as at least 1200, and showed that in one year fifty children died from this disease. The onset in children is acute, and thirst, polyuria and loss of weight are so characteristic that diagnosis is seldom delayed. Sometimes, however, an acute illness like otitis media may precipitate coma in a previously unrecognized case. Diabetes should be remembered in cases of severe vomiting, dehydration, wasting and coma in babies, or of bedwetting and genital pruritus in older children. Recorded urine tests are all-important in diagnosis and management. When heavy sugar is present the nitroprusside test for ketone bodies should be done, and if this is strongly positive the ferric chloride test may confirm the presence of dangerous ketosis.

HOSPITAL TREATMENT

Adequate insulin treatment ensures for the diabetic child a life of normal activity at home and at school, but when the disease is first discovered hospital admission is essential so that from the pattern of clinical progress, glycosuria and glycaemia, a suitable insulin dose can be suggested. With cooperation from intelligent parents many children may be tided over their minor ailments at home, but in all illness attended by continued vomiting, a positive ferric chloride test, pre-coma or coma, immediate admission to hospital is essential.

Team work of a special unit makes hospital treatment easy, but when the child comes home troubles may begin. Instruction of the parents and the child while the child is in hospital makes for good progress, and regular attendance at a diabetic clinic within easy reach of home ensures continued supervision. Some parents find the task too difficult and local education authorities can now arrange residential care for children "handicapped by diabetes". A better phrase would be: "diabetic children handicapped by circumstances through which control of the disease is not possible in their own homes".

DIET

A "free" diet usually means one in which the concentrated carbohydrates such as sugar and jams are forbidden and the carbohydrate intake is un-

of nodular toxic goitres as true neoplasms, a point which still remains unsettled. Other endocrine glands develop benign functioning neoplasms: for instance, the parathyroids and the adrenal cortex.

SUMMARY OF ETIOLOGICAL FACTORS IN THYROTOXICOSIS

The points which have been discussed and are important in considering the problem of the etiology of thyrotoxicosis may be summarized in the following way. There are certain *predisposing factors* which play a primary rôle in preparing the ground for the development of toxicity:—

- (1) Heredity.
- (2) Female sex.
- (3) Environmental factors. These are poorly understood and include such things as emotional stresses. However, it is important to bear in mind the difference between civilian and military populations.

(4) The previous formation of "nodular goitre".

In addition, there are the possible ultimate *precipitating factors*:—

(1) Increased secretion of pituitary thyrotrophin. This is seen in the thyrotoxicosis of acromegalics. It is also probable that it may occur by way of hypothalamic stimuli.

(2) Increased sensitivity of thyroid epithelium to the effect of circulating thyrotrophin.

(3) The interruption of a functional cycle in the gland due to changing conditions in the environment.

(4) The possibility of a lack of antithyrotrophic substance in the patient.

(5) Intrinsic metabolic behaviour of neoplastic tissue. This would include the question of the increased function in certain cases of "nodular toxic goitre".

References

- Bastenie, P. A. (1947): *Lancet*, **i**, 789.
 Brain, W. R. (1948): *Quart. J. Med.*, **7**, 293.
 Campbell, J. M. H. (1924): *Ibid.*, **18**, 191.
 de Robertis, E. (1948): *J. clin. Endocrinol.*, **8**, 956.
 Gardiner-Hill, H. (1929): *Quart. J. Med.*, **22**, 217.
 Harris, G. W. (1948): *Physiol. Rev.*, **28**, 139.
Lancet (1947): **i**, 794.
 Loeser, A. (1937): *Proc. Roy. Soc. Med.*, **30**, 1445.
 Marine, D. (1924): *Medicine*, **3**, 453.
 Means, J. H. (1948): "Thyroid and its Diseases", 2nd edition, London.
 Medical Research Council Memorandum, No. 18 (1948): "Thyroid Enlargement and other changes Related to the Mineral Content of Drinking Water", London.
 Meulengracht, E. (1945): *Acta. med. scand.*, **121**, 446.
 Plummer, H. S. (1928): *Trans. Ass. Amer. Physicians*, **43**, 159.
 Pochin, E. E. (1945): *Clin. Science*, **5**, 75.
 Rawson, R. W. (1948a): "Thyroid and its Diseases" (J. H. Means), 2nd edition, London, p. 118.
 — (1948b): *Ibid.*, p. 446.
 Rundle, F. F., and Pochin, E. E. (1944): *Clin. Science*, **5**, 51.
 Wolff, J., and Chaikoff, I. L. (1948): *Endocrinology*, **42**, 468.

TABLE I

Insulin	Injection	Maximum Effect	Glycosuria					Blood sugar		Insulin Action
			Bed-time	On Waking	Before Breakfast	Before Lunch	Before Lunch	Before Lunch	Before Breakfast	
Protamine Zinc insulin	One before breakfast	Tea-time Over-night	+	++	+ to 0 *	++ to ++	++ to ++	mg. % 250-170	mg. % 170-100	Weak Slow Prolonged Irregular
Soluble Insulin	One before breakfast One before tea	Mid-day meal 4-6 hours after supper	++ to +	0 to ++ *	++ to ++	++ to ++	++ to ++	150-80 *	200-300	Strong Quick Gone in 8 hours Regular
Mixed P.Z.I. and Soluble	One before breakfast	Mid-day meal Tea-time Over-night	++	++	++ to 0 *	++ to ++	++ to ++	250-150 *	170-100	Combines above
Soluble + Mixed P.Z.I. and Soluble	Soluble before breakfast Mixed dose before tea	Mid-day meal	++ to +	++ to +	++ to 0 *	++ to ++	++ to ++	150-80 *	170-120	Soluble action, sharp in morning, blunted and delayed at night

worried by the disease or its treatment, growing at the normal rate, and free from ketone bodies and from serious hypoglycæmia.

In table I, I have tried to express some of the patterns of the action of different combinations of insulin used in children at clinics or residential schools who show these good results.

If specimens of urine are to reflect insulin action around the time of the test, the bladder should have been emptied one hour before. The asterisk indicates tests which are of value as practical guides to treatment.

Protamine zinc insulin alone or in combination with soluble is a poor weapon when very large doses are needed to produce patterns like the above. In the residential schools, children are generally transferred to the single mixed

measured and irregular. The notion that insulin adjustment will give adequate control with such diets is false, for children treated in this way are ill-grown and under-nourished. They alternate between hyperglycæmia with symptoms and severe insulin reactions.

The rules of diet are, in these days, most simple. The carbohydrate should be measured and constant, adequate to the child's needs, and satisfying. Protein and fat may be eaten according to appetite as in normal children. In very young children, often sensitive to the insulin which they invariably need, it is sometimes difficult to give enough carbohydrate to cover insulin action. The following figures give some guide to carbohydrate needs:—

Infancy to 5 years	100-170 g. daily
5-10 years	150-200 g. daily
10-16 years	200-250 g. daily

For the translation of these values into food quantities the reader is referred to the 10 gramme "black" portions of R. D. Lawrence's "Line Ration Scheme" or to his "Simple Diabetic Diet", both of which are included in "The Diabetic A.B.C." (1948). When appetite is poor owing to illness or the caprice of childhood, concentrated soluble carbohydrate, such as sugar or "vitagluco" tablets, may be needed for a brief time to maintain the carbohydrate intake. Simple household measures have largely replaced food weighing in recent years, although most children do better when the concentrated carbohydrates such as bread and cereals are regularly weighed. Sweets are best avoided. Patent diabetic foods are not appreciated, but diabetic chocolate of no carbohydrate value is liked by some children, and Wall's ice cream, reckoned at 10 grammes of carbohydrate to a three-penny block, is beloved by them all.

The distribution of carbohydrate at each meal is arranged to cover insulin action. Typical distributions for active children using the insulin arrangements to be described are:—

	Carbohydrate Grammes		
Breakfast: 7.30-8 a.m.	40 50 60
Morning snack: 10.45-11.15 a.m.	10 20 30
Mid-day meal: noon-1 p.m.	30 50 50
Tea: 4-4.30 p.m.	30 50 60
Bed-time	40 30 50
Total for 24 hours	150 200 250

INSULIN

It must be recognized that with any form of humane treatment it is impossible to maintain a physiological level of the blood sugar (70-150 mg./100 ml. for children) through the day and night. Insulin gives of its best when by its use the child is well, active and happy at home and at school, not

glucose at the times of maximum action.

The low renal threshold in diabetic children.—The renal threshold is the blood sugar level at which the kidney allows glucose to pass into the urine. A lower threshold than the average, 170 mg. of glucose per 100 ml. of blood, is not uncommon in diabetic children, and children with the low threshold may show heavy glycosuria and even ketonuria when the blood sugar is within the normal range. Attempts to regulate insulin dosage by urine tests may then result in disastrous hypoglycæmia. Since much glucose is wasted in glycosuria, high carbohydrate diets are needed to provide for growth and prevent ketonuria. For the child with a very low renal threshold it may be important to test the indicative specimens and maintain glycosuria in them all. The parents of these most difficult diabetics should understand the nitroprusside test, and blood sugar control is the only accurate guide to dosage.

EXERCISE AND HYPOGLYCÆMIA

Exercise always alters the pattern, and hypoglycæmia can no more be avoided than hyperglycæmia, since in the well-controlled child exercise invariably increases the insulin effect. Regulation of activity is undesirable but it is possible to prevent severe reactions by giving extra carbohydrate during exercise. It is wise to give 20 to 30 g. of extra carbohydrate before a swim. Wherever these children go, soluble carbohydrate, such as sugar lumps or vitagucose tablets, must be at hand.

Symptoms of hypoglycæmia vary with the individual but are capricious. Even after years of the usual minor reactions, severe, unwonted symptoms may occur in response to hypoglycæmia. The usual level of the blood sugar at which symptoms occur is 60 mg./100 ml. but many children show little reaction at 40 mg./100 ml. Sometimes hypoglycæmia is betrayed by some alteration in behaviour. Most children learn to recognize the early symptoms and complain of "feeling low". One well-marked but little known symptom of a severe reaction is an intolerable tingling in the lips and tongue. Whether epilepsy is proven or not, a fit in a child taking insulin always suggests hypoglycæmia.

EMERGENCIES

In a child taking adequate insulin, emergencies arise only when carbohydrate cannot be assimilated by reason of vomiting or of hypoglycæmia. *Diabetic coma* is always preceded by at least some hours of illness, but insulin coma is immediate and unheralded by thirst and polyuria or the severe back pain, vomiting and air-hunger of ketosis. The child in diabetic coma is flushed and dry, whereas profound hypoglycæmia causes extreme pallor and sweating. Examination of the urine reveals no heavy ketonuria in insulin coma but glycosuria may be present from glucose retained from a previous phase of hyperglycæmia. Diabetic coma is rare and sometimes fatal. It is never seen at the residential schools. The common story in this needless tragedy is that insulin has been withheld during an attack of vomiting for

dose when doses of protamine zinc insulin approximating to the following fail to give good control:—

Age-group	2-5	5-10	10-15
Units of P.Z.I.	4-10	10-16	16-20

In the mixed dose, soluble insulin is converted into protamine zinc insulin to the extent of about one-half the units of the original protamine zinc content. If, in a mixed dose, the original protamine zinc insulin needs to be much greater than the figures given above, then I often use two doses of soluble insulin. This change is seldom difficult in a group, but may be resisted by the individual child or his parents, and in some cases it may be necessary to continue with such a large mixed dose as 28 units of protamine zinc + 48 units of soluble. When the two doses of soluble fail, I mix a very little protamine zinc insulin (4 to 8 units) with the afternoon soluble. This method, which was described by Lawrence and Oakley (1944), gives very good control, and the addition of protamine zinc insulin blunts and delays the action of the afternoon soluble, but often gives sharp hypoglycæmic reactions around noon.

Frequency of tests and alteration of doses.—The urine should always be tested when the child is ill. For children in good health at the residential schools two specimens are tested as a routine on two days in each week, and the records, which include times of insulin reactions and clinical details, are so helpful in assessing dosage that blood sugar tests are not often needed.

Regulation of dosage is easiest with two doses of soluble insulin. The afternoon dose is usually lower than the morning one as its effect is less covered by carbohydrate, e.g. doses of 16/12 and 40/28. The morning effect is best seen in the urine specimen before the mid-day meal, and the waking specimen indicates to some extent the effect of the second dose. If heavy glycosuria persists the doses are increased by 2 units and, when the child is well, it is usually best to allow two days between changes.

With protamine zinc insulin the indicative specimen is the one before breakfast, the bladder having previously been emptied on waking, and at least three days should elapse between successive changes. In the single mixed dose the effect of the soluble component is seen before the mid-day meal and of the delay insulin in the specimen before breakfast, provided the bladder has previously been emptied on waking. Hypoglycæmic reactions may call for reduction of dosage, and here again the consideration of the times of maximum action of the two insulins is a useful guide.

Insulin changes in illness.—Whenever the diabetes is upset by illness, extra soluble insulin is most useful. If a child on the single mixed dose shows ketonuria with heavy glycosuria, a temporary tiny dose—4 to 12 units—of soluble before tea is often helpful. If real difficulties arise, a temporary change to soluble insulin is indicated. The effect of each dose is greatest at four to six hours and gone in eight hours, so that the effect of each single dose can be estimated and covered with carbohydrate. All surgical procedures are managed very easily if soluble insulin is used and covered by

THE PROBLEM OF PRODUCTION OF STEROID HORMONES

By E. C. DODDS, M.V.O., M.D., D.Sc., F.R.C.P., F.R.S.

*Courtauld Professor of Biochemistry, University of London; Director, Courtauld
Institute of Biochemistry, Middlesex Hospital.*

ALTHOUGH a great deal is known to-day about the effects of administering sex hormones, little is known by the people who use them of the methods of their preparation. Behind preparations such as œstradiol benzoate, testosterone propionate, progesterone, and so forth, lies a fascinating story which it is proposed to outline in this article.

THE EVOLUTION OF HORMONE THERAPY

Looking back on the therapeutic use of sex hormones, it can be stated that this really dates from about the early and middle 1930's, and the inquirer will wonder why these common substances were not available until this date. On looking into the history this is the more astonishing, since the association of the ovaries with the secondary sexual characteristics has been known from time immemorial, and the preparation of active extracts of the ovaries has been known for the last forty years. Reference to the literature shows a number of early names which are now forgotten except by specialists. Knauer in 1900 showed that the effects of spaying could be overcome by transplanting an ovary from another animal. Attempts to treat the climacteric by the administration of dried ovaries were attended with very doubtful results, and after a certain popularity in the early part of the century this method fell into disrepute. The first really scientifically controlled observations were made by Adler in 1912. By injection of watery extracts of ovaries he was able to produce typical signs of œstrus in animals, which he confirmed by histological investigations of the uterine mucosa.

Chemical preparations of ovarian extract were made by Iscovesco (1912), Fellner (1912, 1913), and Seitz, Wintz and Fingerhut (1914). In 1915, Herrmann published his method, by which we now know œstrone in crude form would be obtained. This consisted in extracting the ovary with volatile solvents and precipitating the phospholipins with acetone, thus obtaining an oil of fairly high activity. When this was injected into female animals out of the rutting season, rutting symptoms were produced. The material was actually marketed and sold over a long period. Why is it, then, that we had to wait until the 1930's before the material came into common use? The reason, as we now know, was lack of efficient dosage. In modern terms the dosage administered by Herrmann was equivalent to only a fraction of what is now known to be required to produce objective signs in women, and even if sufficient dosage of active material could have

fear of hypoglycæmia.

Vomiting.—Insulin must always be continued, and it is quite safe to give the usual dose of soluble or the soluble component of the mixed dose. Glucose drinks of the carbohydrate value of the usual meals (two table-spoonsful of glucose = 30 g. carbohydrate) should be given and, if these are not retained, admission to hospital is essential. The vomiting must be stopped by gastric lavage, and soluble insulin with glucose at four-hourly intervals may be needed to abolish ketosis. If these simple measures fail, intravenous glucose saline by continuous drip must be given. For the treatment of diabetic coma the reader is referred to "The Diabetic Life" (Lawrence, 1945).

Insulin coma.—Intravenous injection of 20 to 40 ml. of 30 or 50 per cent. sterile glucose solution is the most effective treatment for insulin coma. Veins may be difficult to find in the youngster but glucose, 30 g. dissolved in water, can be given by stomach-tube. The urine should be tested at four-hourly intervals after recovery and insulin should not again be given until heavy glycosuria appears. For some hours afterwards frequent generous feeds of carbohydrate may be needed to maintain the blood sugar. In the absence of ketosis, hyperglycæmia does no immediate harm, and a reduction of insulin dosage is indicated after single major or repeated minor reactions.

PROGNOSIS

Without insulin these children will die. The lives and education of children whose diabetes cannot be controlled at home can be preserved by residential care. With insulin we hope that even the normal healthy span will be allowed to diabetic children, but after twenty-five years of controlled diabetes a fair number of them will show some degree of albuminuria, some hypertension, or some abnormalities of the retinal vessels. The clinical significance of these late changes is not clear, but they must be mentioned to stress the importance of careful treatment in the formative years of childhood.

SUMMARY

(1) With good control the nitroprusside test remains negative but glycosuria, hyperglycæmia, and occasional hypoglycæmic reactions cannot be avoided by present methods of treatment of the active diabetic child. (2) Continued vomiting and dangerous ketosis, as shown by the ferrie chloride test, are grave emergencies requiring immediate treatment in hospital. (3) No single dose of insulin must ever be interrupted except during insulin coma. (4) The urine and blood tests of each individual show a pattern which is judged in relation to times of action of the insulin arrangement. (5) The assessment of control includes clinical observation of the well-being and rate of growth of the child.

References

- Henderson, P. (1949): *Brit. med. J.*, i, 478.
 Lawrence, R. D. (1945): "The Diabetic Life," 13th edition, London.
 — (1948): "The Diabetic A.B.C.," 10th edition, London.
 — and Oakley, W. G. (1944): *Brit. med. J.*, i, 422.

pause, it was of no value in the treatment of amenorrhœa. The importance of the corpus luteum hormone had been recognized in biological circles for many years, and in 1929 Corner and Allen were able to produce an active extract which would produce in the ovariectomized monkey a genuine menstrual cycle as proved by curettage. Later, similar results were obtained in ovariectomized women, and it was clearly demonstrated that correctly

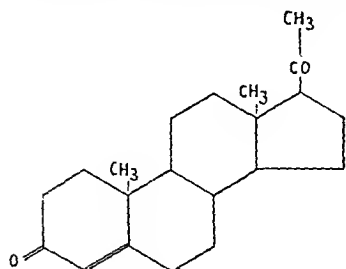


FIG. 3.—Progesterone

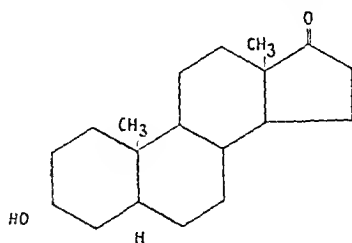


FIG. 4.—Androsterone

spaced dosage with œstradiol benzoate and the corpus luteum hormone, or progesterone (figure 3) as it was subsequently called, was capable of producing every phase of the menstrual cycle. This could be checked histologically by examination of the endometrium. It appeared that the corpus luteum hormone would be useful in various conditions such as threatened abortion and certain forms of menorrhagia, but the supply position here at once became acute. The hormone had been isolated in pure crystalline form in 1934 by four independent groups of investigators, but there was no adequate supply of corpora lutea and for a number of years the material was scarce and expensive. Again, I shall indicate later the way in which this problem was solved.

Testosterone.—The next sex hormone to emerge from the laboratory into clinical practice was that of the testis. This has a very similar history to that

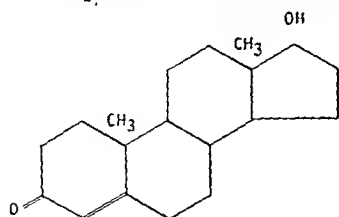


FIG. 5.—Testosterone

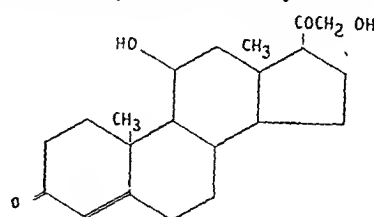


FIG. 6.—Corticosterone

of the œstrus-producing hormone. It had been known practically for all time that the male secondary sexual characteristics depend upon the integrity of the testes, and the first replacement therapy was performed by Berthold in 1849, who succeeded in producing growth of the comb in capons by injecting crushed testes. A male sex hormone was isolated from normal male urine by Butenandt (1931) and this substance was called androsterone (figure 4). It was found that whilst this was capable of producing comb

been given, the contaminants were such as to produce severe secondary reactions. No progress could be made until fractionation of the material could be effected so that toxic contaminants could be avoided.

It is not proposed to go over the story of the discovery of what we now know as *œstrone*. Introduction of the vaginal smear method of assay by Allen and Doisy (1923) was one of the turning points. The second turning point was the discovery of the presence of *œstrogenic* material in the urine of pregnancy by Aschheim and Zondek in 1927. The extraction of the steroid in 1929 and 1930 (Butenandt *et al.*, 1934; Doisy *et al.*, 1929; Marrian, 1930) completed the picture from the point of view of chemical characterization. The production of *œstrone* from 1930 onwards was relatively simple. The urine of pregnant mares was collected, mainly in Germany and in France, and was transported to central factories where it was concentrated, and the concentrated urine was extracted with suitable solvents. The solvent was evaporated, leaving a crude oil of high *œstrogenic* potency. This was purified originally by a process of high vacuum distillation, and from the appropriate fraction *œstrone* could be obtained in crystalline form.

The formula of *œstrone* is given in figure 1. It was soon demonstrated

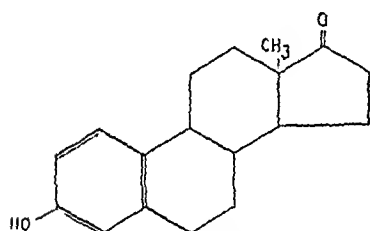


FIG. 1.—*Œstrone*

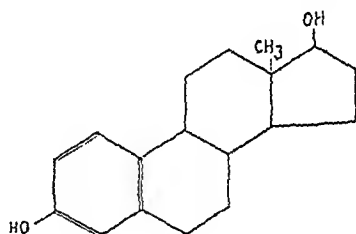


FIG. 2.—*Œstradiol*

(Schwenk and Hildebrandt, 1933) that if this be subjected to reduction in the chemical laboratory the ketone group on the carbon atom 17 is converted into a secondary alcohol and a new compound known as *œstradiol* (figure 2) is produced. Now, in order to slow up the absorption of these substances the hydroxyl group in the 3-position is esterified, usually with benzoic acid, and the final clinical material is either *œstrone* benzoate or *œstradiol* benzoate. This is put up in oil in ampoules and injected intramuscularly.

Up to the outbreak of the war the urine of pregnant mares was a plentiful source of supply for the *œstradiol* benzoate used in clinical work, but this source quickly began to diminish as the war proceeded, and towards the end of the war, in Europe at least, the collection of pregnant mares' urine became impossible, and again, the actual number of mares fell so that an entirely new source of supply had to be looked for. I shall return to this later.

Progesterone.—After the introduction of *œstradiol* benzoate it was felt, for a short time at least, that all the requirements of replacement therapy in women were supplied by this substance. However, whilst it was found that *œstradiol* could be used to treat infantilism and the symptoms of the meno-

cyclohexane rings, such as a hydroxyl group in the 3-position, these can have various relationships to the points of the ring and also to any other groups, such as an angle methyl group.

Natural œstrogens contain from two to six centres of asymmetry, resulting in 4 to 64 possible isomers. The hormones, progesterone, testosterone and

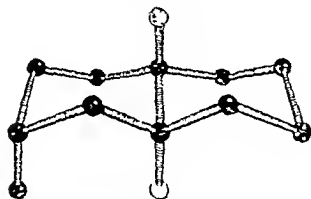


FIG. 10.

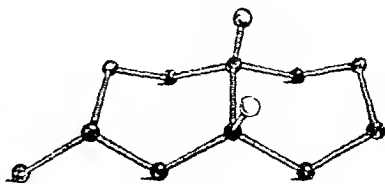


FIG. 11.

corticosterone contain fully saturated and partially saturated rings, so that in these hormones also, a large number of isomers is possible. It follows therefore that the synthesis of all these substances presents enormous difficulties.

THE IMPORTANCE OF CHOLESTEROL

The production of these hormones has been made possible by a particularly interesting application of the methods of organic chemistry. It is necessary for a moment to digress on the chemistry of cholesterol, the sterol present in all animal tissues, and representing a group of substances present in nature, for example, in plants as phytosterols. Years of research, dating from last century, have been put in, in an attempt to solve the constitution of this substance. This was finally accomplished in about 1932, and figure 12 shows the formula. To many the half century of research that was devoted to the establishment of this constitution must have seemed academic

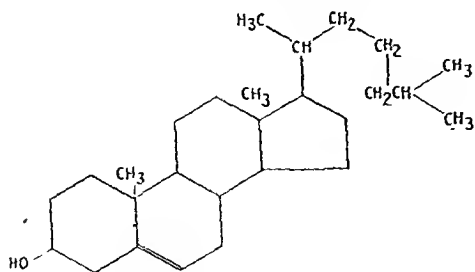


FIG. 12.—Cholesterol

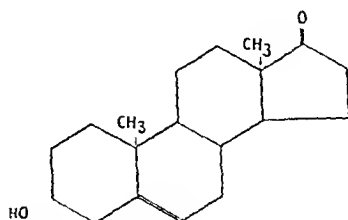


FIG. 13.—Dehydroandrosterone

in the extreme, and it must also be admitted that those men who devoted their lives to this study certainly had no inkling of the important practical work that they were undertaking.

If cholesterol be oxidized with chromic acid, the side-chain on the 17-carbon atom is split off and one is left with the aliphatic moiety and the ring system. To Ruzicka (1934) belongs the credit of recognizing that the

growth in capons it was not as potent as some unpurified extracts of the testis. Later it was shown that the testis secretes a different substance, testosterone (David *et al.*, 1935) (figure 5). The isolation of testosterone is a complicated procedure and testes are not an economic source of supply.

Finally, there is an exactly parallel story with the suprarenal cortex, leading to the isolation of a number of compounds such as corticosterone (figure 6). Again the isolation is a difficult procedure and the yields are extremely small. We were therefore faced with a production problem of all these substances, including even œstradiol, during the war.

SYNTHESIS

In the first instance, total synthesis is out of the question as a practical proposition. Through the brilliant work of Anner and Miescher (1948) œstrone has been totally synthesized, but whilst this represents a great triumph of organic research, it is in no way possible as a commercial procedure. In order to appreciate the difficulties of synthesis in this field, it is necessary for the reader to understand that the mere stringing together of the carbon atoms in the form of the cyclo-penteno-phenanthrene ring system (figure 7) represents only a minor part of the complications. Space does not permit of a detailed description of the stereochemical problems

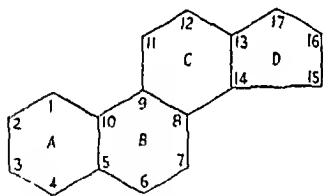


FIG. 7.—Cyclopenteno-phenanthrene

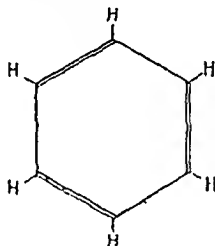


FIG. 8.—Benzene

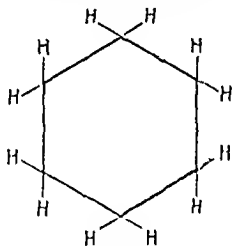


FIG. 9.—Cyclohexane

involved, but it is essential to appreciate the principles. Put briefly, it can be said that a benzene ring is a relatively simple structure and can be represented by the illustration figure 8. The three double bonds ensure that the molecule falls all on one plane, and the hydrogen atoms around it are arranged above and below this particular plane of the ring. A very different state of affairs occurs if we saturate this benzene ring and have the corresponding fully hydrogenated substance, cyclohexane (figure 9). If we join two benzene rings together we still have them on the same plane, but if we join two cyclohexane rings together we then get a number of possibilities in the spatial arrangement of the carbon atoms. Briefly speaking, they can be arranged in two ways: one in which the points of the saturated rings are in opposite planes, in which case the rings will take the appearance of a chair; alternatively, the points can be in the same plane, thus giving the appearance of two beds. This is clearly shown by the perspective diagrams (figures 10, 11). It is obvious that if groups are attached to these two fused

injecting compound E into patients with rheumatoid arthritis and acute rheumatic fever. The original observation was made by Hench *et al.* (1949), who maintained that it was necessary to give 100 mg. a day of this substance. It is stated that desoxycorticosterone and corticosterone itself are without action on rheumatoid arthritis. Owing to the prevalence of the disease, it can easily be seen that vast quantities of this compound would be required to treat all the cases of rheumatoid arthritis in the world. Production on this scale is an impossibility at the moment. The isolation of the compound from the suprarenal cortex is out of the question, in view of the small yield, and unfortunately it cannot be produced by the method of degradational synthesis from cholesterol already described. The only possibility at present is to use deoxycholic acid (figure 17) as a starting material. This has a polar

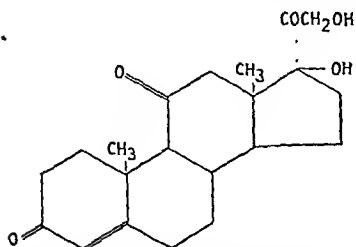


FIG. 16.—Kendall's Compound E
(17-hydroxy-11-dehydro-corticosterone)

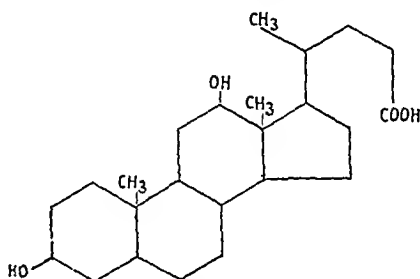


FIG. 17.—Deoxycholic acid

group at position 12, and by suitable chemical manipulation it is possible to induce this group to migrate to position 11. Deoxycholic acid can be prepared from bile, but its conversion into compound E requires some thirty stages of synthesis, with minute yields in the final stages. This means that we start with a raw material very limited in supply, the conversion of which into the therapeutic agent gives only minute yields. The production problem of this compound therefore presents one of the most formidable tasks with which the organic chemist has ever been confronted.

THE SYNTHETIC ŒSTROGENS

In conclusion, one other method may be mentioned of solving the production problem in relation to certain of the steroid hormones. This is by

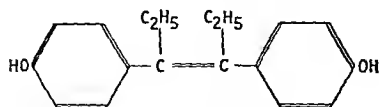


FIG. 18.—Stilboestrol

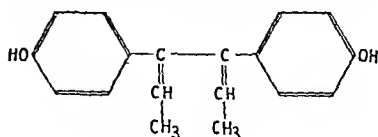


FIG. 19.—Dienoestrol

the production of synthetic analogues. This has been successful only in the case of the œstrogens. The first synthetic œstrogens were prepared in my laboratories in the early 1930's, and a long series of researches led finally

ring system residue left after chromic acid oxidation can be used as a starting point for the synthesis of the steroid hormones. It is fortunate that the stereochemical arrangement of the ring system in cholesterol is the same as that in the steroid hormones, and therefore if one can isolate the nucleus after chromic acid oxidation, one has a substance which can be converted into all the steroid hormones. This is the standard method of manufacture to-day, and consists principally of taking cholesterol and heating it with chromic acid. From the resulting mixture the substance dehydroandrosterone (figure 13) is obtained. This can be subjected to various chemical processes in which double bonds are shifted about in the molecule, and hydroxyl groups, for example, in position 3, converted into ketone groups. To-day all the material used in the clinics is obtained from dehydroandrosterone; thus the supply of progesterone and testosterone originally comes from cholesterol.

A very difficult synthesis is the conversion of dehydroandrosterone to œstrone. This necessitates the aromatization of ring A and, what is more difficult, the removal of the angle methyl group between rings A and B. This has been accomplished, and to-day large quantities of œstrone and subsequently œstradiol, are prepared in this way.

THE CORTICAL HORMONES

The cortical hormones, corticosterone (figure 6) and dehydrocorticosterone (figure 14), differ from all the others in that they have either a hydroxyl or a ketone group in the 11-position. It is possible to convert dehydroandrosterone into the compound known as desoxycorticosterone (figure 15). The acetate of this compound is used in clinical practice and is known as

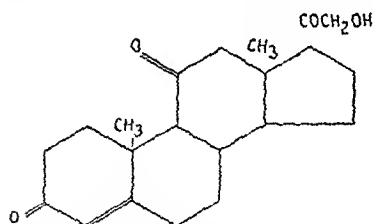


FIG. 14.—Dehydrocorticosterone

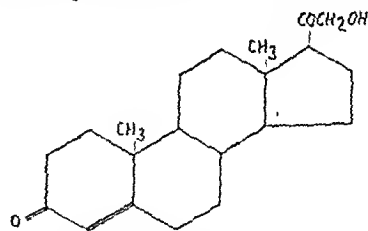


FIG. 15.—Desoxycorticosterone

D.O.C.A. This is, in fact, corticosterone minus the hydroxyl group at position 11. Fortunately, it has been found to possess a number of the biological activities of the cortical hormone and therefore can be used in clinical work. The introduction of a hydroxyl group at position 11 is a formidable procedure and certainly could not be undertaken commercially.

Until comparatively recently there was no practical demand for the large-scale production of substances of this type, but the whole picture has been changed by the introduction of "compound E" of Kendall (Mason, Myers and Kendall, 1936) (figure 16) in the treatment of rheumatoid arthritis. The American literature is flooded with accounts of the miraculous effect of

œstrone and possesses the advantage of being highly active when given by mouth.

GENERAL CONCLUSIONS

From what has been described it can be seen that there are adequate methods of producing quantities of œstrogenic and androgenic substances at reasonable prices. Methods for the production of corticoid and progestational substances do not give such good yields, and therefore these compounds are at present more expensive. The methods are continuously being improved and we can confidently look forward to the time when all substances in the steroid and hormone group will be available for general clinical work. This is perhaps rather a bold prophesy in the case of cortisone, and it would certainly seem at the present time that this presents the most difficult problem for the research worker and manufacturer.

Figures 10 and 11 are reproduced by permission of the Editor of the *Annals of the Royal College of Surgeons*.

References

- Adler, F. (1912): *Arch. Gynæk.*, 95, 349.
 Allen, E., and Doisy, E. A. (1923): *J. Amer. med. Ass.*, 81, 819.
 Allen, W. M., and Wintersteiner, O. (1934): *Science*, 80, 190.
 Anner, G., and Miescher, K. (1948): *Experimentia*, 4, 251.
 Aschheim, S., and Zondek, B. (1927): *Klin. Wschr.*, 6, 1322.
 Butenandt, A. (1929): *Naturwiss.*, 17, 879.
 — (1931): *Z. angew. Chem.*, 44, 905.
 —, Westphal, U., and Hohlweg, W. (1934): *Z. physiol. Chem.*, 227, 84.
 Corner, G. W., and Allen, W. M. (1929): *Amer. J. Physiol.*, 88, 326.
 David, K., et al. (1935): *Z. physiol. Chem.*, 233, 281.
 Dodds, E. C., et al., (1938): *Nature*, 141, 274.
 Doisy, E. A., Veler, C. D., and Thayer, S. A. (1929): *Amer. J. Physiol.*, 90, 329.
 Fellner, O. O. (1912): *Zbl. allg. Path. path. Anat.*, 23, 673.
 — (1913): *Arch. Gynæk.*, 100, 641.
 Hartmann, M., and Wettstein, A. (1935): *Helv. chim. Acta.*, 17, 878, 1365.
 Hensch, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F. (1949): *Proc. Mayo Clin.*, 24, 181.
 Herrmann, E. (1915): *Möschl. Geburtsh. Gynæk.*, 41, 1.
 Horeau, A., and Jacques, J. (1947): *C. R. Acad. Sci., Paris*, 224, 862.
 Inhoffen, H. H., and Hohlweg, W. (1938): *Naturwiss.*, 26, 96.
 Iscovesco, H. (1912): *C. R. Soc. Biol., Paris*, 73, 16.
 Knauer, E. (1900): *Arch. Gynæk.*, 60, 322.
 Marrian, G. F. (1930): *Biochem. J.*, 24, 435, 1021.
 Mason, H. L., Myers, C. S., and Kendall, E. C. (1936): *J. biol. Chem.*, 114, 613; 116, 267.
 Miescher, K., et al. (1944): *Helv. chim. Acta.*, 27, 1727.
 —, — (1946): *Ibid.*, 29, 586, 1231.
 Ruzicka, L., et al. (1934): *Ibid.*, 17, 1395.
 Schwenk, E., and Hildebrandt, F. (1933): *Naturwiss.*, 21, 177.
 Seitz, L., Wintz, H., and Fingerhut, L. (1914): *Münch. med. Wschr.*, 61, 1657, 1734.
 Slotta, K. H., Rushig, H., and Fels, E. (1934): *Beitr. deutsch. chem. Ges.*, 67, 1270, 1624.

to the production of stilbæstrol in 1938. This was done in collaboration with Sir Robert Robinson and his team of workers at the Dyson Perrins Laboratory, Oxford. The formula of stilbæstrol is shown in figure 18, and two other substances, diencæstrol (figure 19) and hexæstrol (figure 20), have also been used clinically. These substances possess the advantage of being very cheap to make and of being highly active by mouth, whereas the

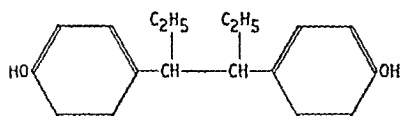


FIG. 20.—Hexæstrol

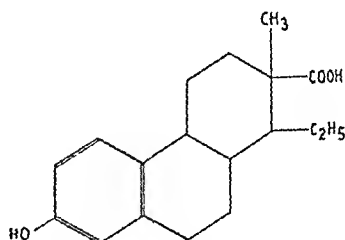


FIG. 21.—Doisylic acid

naturally occurring substances must be administered either subcutaneously or intramuscularly. A large number of synthetic æstrogens has been prepared, and in addition to the stilbæstrol series there is the doisylic acid series, introduced by Miescher and his colleagues (1944, 1946) (figures

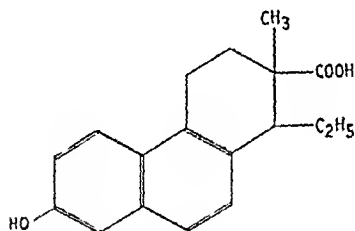


FIG. 22.—Bis-dehydro-doisylic acid

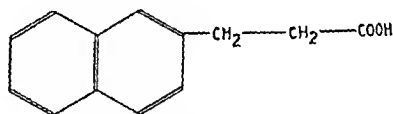


FIG. 23.—Allenolic acid

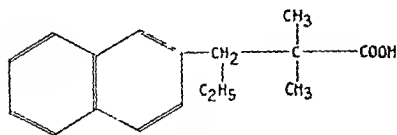


FIG. 24.—Dimethyl-ethyl-allenolic acid

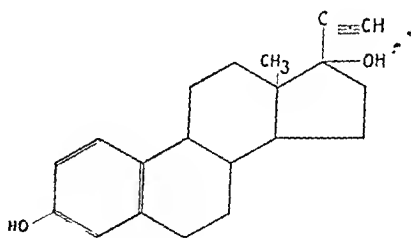


FIG. 25.—Ethinyl æstradiol

21 and 22), and also the allenolic acids introduced by Horeau and Jacques (1947) (figures 23 and 24). There is still one further type which is a modified form of æstradiol, namely ethinyl æstradiol (figure 25) (Inhoffen and Hohlweg, 1938). This substance is produced by chemical treatment of

chorionic gonadotrophin. The question of hormone assays in cases of testicular tumours will be taken up in more detail later.

From the therapeutic standpoint, three types of gonadotrophin have been employed: pituitary gonadotrophin, in the form of an extract of ox or sheep anterior pituitary lobes; chorionic gonadotrophin, derived from the urine of pregnant women; and pregnant mares' serum gonadotrophin, also known as equine gonadotrophin. Regarding the first of these, until recently no reliable pituitary gonadotrophin was available, but from America there has come a report within the last few months of the use of a potent, partially purified, preparation from sheeps' anterior lobes having a predominantly

TABLE I
THE GONADOTROPHINS

Name of gonadotrophin	Source	Actions
Pituitary gonadotrophin (a) F.S.H. (b) L.H. (c) luteotrophic hormone	β cells of anterior lobe of pituitary.	(a) Follicle stimulation in the ovary: stimulation of spermatogenesis in the testis. (b) Formation of corpus luteum in ovary: secretion of androgens by interstitial cells of testis. (c) Maintenance of corpus luteum and secretion of progesterone (doubtful). Mainly luteinizing.
Chorionic gonadotrophin	Chorio-placental system (infertile endometrium). Found in the urine of pregnant women.	Secretion of oestrogens by ovary. These two fractions may be an artefact.
Serum or equine gonadotrophin	Endometrial cups of mares' placenta. Found in the serum of pregnant mares.	Mainly follicle-stimulating.
Tumour gonadotrophin	Certain malignant tumours, chiefly chorio-epitheliomas.	Similar to that of chorionic gonadotrophin.

follicle-stimulating action (Jungck *et al.*, 1949). There is no international standard of potency for pituitary gonadotrophin. International standards exist for chorionic gonadotrophin and for equine gonadotrophin. This latter, although analogous in origin to human chorionic gonadotrophin, has a quite different action, being mainly follicle-stimulating. Finally, there exist preparations consisting of chorionic gonadotrophin mixed with pituitary gonadotrophin ("synapoidin", Parke Davis; "ambinon A", Organon); for these mixed gonadotrophins there is of course no international standard.

Table I summarizes the nature of the gonadotrophins.

GONADOTROPHIN ASSAY

Principles and methods of gonadotrophin assays.—Gonadotrophin assays may

THE PRESENT CLINICAL STATUS OF GONADOTROPHINS

By G. I. M. SWYER, D.M., D.Phil., M.R.C.P.

Endocrinologist, University College Hospital Medical School.

THE interest of the clinician in gonadotrophins is properly confined to two aspects, namely, the diagnostic value of gonadotrophin assays and the therapeutic value of gonadotrophin administration. With the problem of the nature and number of gonadotrophins he is less directly concerned, although for a clear understanding of the former aspects some consideration of the latter is necessary. A brief account will therefore be given of this theoretical problem, to be followed by a more extensive treatment of the practical side of the subject.

THE NATURE AND NUMBER OF GONADOTROPHINS

The gonadotrophins may be defined as protein hormones, the principal actions of which are exerted upon the gonads, wherein they produce specific growth changes. They originate from two main sources; the basophil cells of the anterior lobe of the pituitary gland and the chorio-placental system; in addition, certain tumours, principally chorio-epitheliomas, secrete gonadotrophins. There is no doubt that the gonadotrophins from these sources are different; whether pituitary gonadotrophin is a single substance or whether, according to the classical view, there are two pituitary gonadotrophins, *follicle-stimulating hormone*, *F.S.H.*, and *lutinizing hormone*, *L.H.* (interstitial-cell-stimulating hormone, *I.C.S.H.*, is synonymous with *L.H.*) is still a matter of debate and beyond the scope of this article. What is true, however, is that by fractionation procedures, apparently pure proteins may be obtained from the anterior pituitary having follicle-stimulating and luteinizing activities respectively, although it is still uncertain whether these substances exist preformed or are the products of chemical manipulations in the laboratory. In addition, a third pituitary gonadotrophin, *luteotrophic hormone*, the function of which is to maintain the corpus luteum, produced by the action of luteinizing hormone, and to stimulate the secretion of progesterone, is also described; it is apparently the same substance as prolactin. The gonadotrophin produced by the chorio-placental system is usually termed *chorionic gonadotrophin* (*C.G.*), although some believe that it originates from the maternal tissues only—in fact, the endometrium (Gordon, 1949). Its action is largely luteinizing, although it is certainly not the same substance as pituitary luteinizing hormone. The gonadotrophin secreted by certain tumours also has a luteinizing action, but again is quite probably a different substance from

hormone. For the quantitative assay of luteinizing gonadotrophin, criteria such as the increase in ovarian and uterine weight in the immature female rat or the increase in weight of the prostate and seminal vesicles of the immature male rat may be used. An interesting method involving the use of oestrogenized male cocks (Nalbandov and Baum, 1948) has been evolved recently, and by this means the presence of both follicle-stimulating and luteinizing activity can be differentiated, although not differentially assayed.

Except when the gonadotrophin is present in particularly large amounts, as in pregnancy and in the presence of certain testicular tumours, resort to methods of extracting and concentrating the excreted hormone is necessary. Twenty-four hour urine collections must be made and the treatment may then follow one of two main lines: the gonadotrophin may be precipitated by means of alcohol, tannic acid or benzoic acid and then further prepared so as to be suitable for injection into the test animals in graded doses; or the urine may be passed through a large ultrafilter, the protein constituents (including the gonadotrophins) being retained on the collodion membrane, which is removed and dissolved in an acetone-ether mixture from which the active material is recovered by centrifugation. Provided the apparatus is available, the latter is by far the more convenient of the two procedures.

CLINICAL VALUE OF GONADOTROPHIN ASSAYS

The principal reason for referring in some detail to the technical side of gonadotrophin assays is to emphasize the fact that they are not to be undertaken too lightly, and to point out that whereas the crude qualitative tests, such as the Aschheim-Zondek, Friedman or male-toad test, are relatively simple matters, the quantitative assays are an entirely different proposition. It is therefore pertinent to inquire what value these procedures may have for the clinician, and particularly when qualitative methods no longer serve but must be supplemented by the more complicated quantitative assays. With the *diagnosis of pregnancy* we need scarcely concern ourselves; highly accurate results are obtained from all the qualitative procedures in common use. The major *complications of pregnancy* associated with altered gonadotrophin excretion may similarly be dealt with in summary fashion: hydatidiform mole and chorio-epithelioma are usually associated with exaggerated outputs of chorionic gonadotrophin, so that the Friedman test is generally (but *not* always) positive in dilutions of 1 in 100 or more. What is sometimes forgotten is that the natural gonadotrophin peak (reached about the tenth week of gestation) and the increase of gonadotrophin excretion in multiple pregnancies may also give a positive Friedman test in high dilutions and so enhance the erroneous suspicion of hydatidiform mole, if other suggestive signs and symptoms are present. A case for quantitative chorionic gonadotrophin assays might be made out on the basis of the claims put forward by the Smiths (1948) that the gonadotrophin excretion is increased in patients with late toxæmia of pregnancy, and that this increase has a prognostic

be carried out with serum or urine, the latter being most commonly employed. So many different techniques have been described, not only for preparing the extracts but also for testing them, that detailed description is quite beyond the scope of this article. It may be said, in the first place, that hitherto bio-assay has been the only available procedure and that most of the reports in the literature show the grave defect of using animal units rather than assay in terms of standard substances. As a result, comparison of the findings in one laboratory with those of another is often misleading. Accurate bio-assay, it must be emphasized, is difficult, time-consuming, and cannot be accomplished except with relatively large numbers of animals. It is possible that more convenient methods based on immunochemical principles may become available in the future.

The first of the well-known assay procedures, the test of Aschheim and Zondek (1928), was advanced as a qualitative test for the detection of the anterior-pituitary-like substance, now called chorionic gonadotrophin, present in pregnancy urine, and a good deal of the confusion that has arisen in the sphere of hormone assays in cases of testicular tumours is the result of attempts to use it in a *quantitative* manner. It consists in the production of ovulation in immature mice following repeated injections of the urine to be tested. Friedman (1929) showed that a single intravenous injection of the urine of pregnancy would cause ovulation in the rabbit, and upon this has been based the test known by his name. This test is again qualitative only, indicating the presence of some 15 to 20 I.U. or more of chorionic gonadotrophin in the quantity of urine injected; by means of serial dilutions a semi-quantitative test can be obtained. More recently, a number of other tests for the same purpose have been devised, the main object being a decrease in time taken to complete the test and a simplification of the manipulations; external ovulation in the South African clawed toad (*Xenopus laevis*), hyperæmia of the immature rat ovary, and the passage of spermatozoa into the cloaca in various male batrachians (notably the South American toad *Bufo arenarum* Hensel, the North American leopard frog *Rana pipiens*, and, apparently, the common British toad *Bufo vulgaris*) have been the criteria of a positive response, the time required for its production reaching the low level of less than three hours in the last of these tests.

All the above tests detect chorionic gonadotrophin, the action of which, as previously stated, is mainly luteinizing; they will not detect the gonadotrophin excreted in the urine of males and of non-pregnant women, which has a follicle-stimulating action. For this purpose criteria such as the increase in ovarian weight, the causation of vaginal opening or the production of vaginal cornification, all in immature rats or mice, can be used. It must, however, be emphasized that since chorionic gonadotrophin will also produce these effects, it is technically a most difficult (or even impossible) procedure to assay follicle-stimulating hormone in the presence of considerable amounts of chorionic gonadotrophin or other mainly luteinizing

hormone. For the quantitative assay of luteinizing gonadotrophin, criteria such as the increase in ovarian and uterine weight in the immature female rat or the increase in weight of the prostate and seminal vesicles of the immature male rat may be used. An interesting method involving the use of oestrogenized male cocks (Nalbandov and Baum, 1948) has been evolved recently, and by this means the presence of both follicle-stimulating and luteinizing activity can be differentiated, although not differentially assayed.

Except when the gonadotrophin is present in particularly large amounts, as in pregnancy and in the presence of certain testicular tumours, resort to methods of extracting and concentrating the excreted hormone is necessary. Twenty-four hour urine collections must be made and the treatment may then follow one of two main lines: the gonadotrophin may be precipitated by means of alcohol, tannic acid or benzoic acid and then further prepared so as to be suitable for injection into the test animals in graded doses; or the urine may be passed through a large ultrafilter, the protein constituents (including the gonadotrophins) being retained on the collodion membrane, which is removed and dissolved in an acetone-ether mixture from which the active material is recovered by centrifugation. Provided the apparatus is available, the latter is by far the more convenient of the two procedures.

CLINICAL VALUE OF GONADOTROPHIN ASSAYS

The principal reason for referring in some detail to the technical side of gonadotrophin assays is to emphasize the fact that they are not to be undertaken too lightly, and to point out that whereas the crude qualitative tests, such as the Aschheim-Zondek, Friedman or male-toad test, are relatively simple matters, the quantitative assays are an entirely different proposition. It is therefore pertinent to inquire what value these procedures may have for the clinician, and particularly when qualitative methods no longer serve but must be supplemented by the more complicated quantitative assays. With *the diagnosis of pregnancy* we need scarcely concern ourselves; highly accurate results are obtained from all the qualitative procedures in common use. The major *complications of pregnancy* associated with altered gonadotrophin excretion may similarly be dealt with in summary fashion: hydatidiform mole and chorio-epithelioma are usually associated with exaggerated outputs of chorionic gonadotrophin, so that the Friedman test is generally (but *not* always) positive in dilutions of 1 in 100 or more. What is sometimes forgotten is that the natural gonadotrophin peak (reached about the tenth week of gestation) and the increase of gonadotrophin excretion in multiple pregnancies may also give a positive Friedman test in high dilutions and so enhance the erroneous suspicion of hydatidiform mole, if other suggestive signs and symptoms are present. A case for quantitative chorionic gonadotrophin assays might be made out on the basis of the claims put forward by the Smiths (1948) that the gonadotrophin excretion is increased in patients with late toxæmia of pregnancy, and that this increase has a prognostic

be carried out with serum or urine, the latter being most commonly employed. So many different techniques have been described, not only for preparing the extracts but also for testing them, that detailed description is quite beyond the scope of this article. It may be said, in the first place, that hitherto bio-assay has been the only available procedure and that most of the reports in the literature show the grave defect of using animal units rather than assay in terms of standard substances. As a result, comparison of the findings in one laboratory with those of another is often misleading. Accurate bio-assay, it must be emphasized, is difficult, time-consuming, and cannot be accomplished except with relatively large numbers of animals. It is possible that more convenient methods based on immunochemical principles may become available in the future.

The first of the well-known assay procedures, the test of Aschheim and Zondek (1928), was advanced as a qualitative test for the detection of the anterior-pituitary-like substance, now called chorionic gonadotrophin, present in pregnancy urine, and a good deal of the confusion that has arisen in the sphere of hormone assays in cases of testicular tumours is the result of attempts to use it in a *quantitative* manner. It consists in the production of ovulation in immature mice following repeated injections of the urine to be tested. Friedman (1929) showed that a single intravenous injection of the urine of pregnancy would cause ovulation in the rabbit, and upon this has been based the test known by his name. This test is again qualitative only, indicating the presence of some 15 to 20 I.U. or more of chorionic gonadotrophin in the quantity of urine injected; by means of serial dilutions a semi-quantitative test can be obtained. More recently, a number of other tests for the same purpose have been devised, the main object being a decrease in time taken to complete the test and a simplification of the manipulations; external ovulation in the South African clawed toad (*Xenopus laevis*), hyperæmia of the immature rat ovary, and the passage of spermatozoa into the cloaca in various male batrachians (notably the South American toad *Bufo arenarum* Hensel, the North American leopard frog *Rana pipiens*, and, apparently, the common British toad *Bufo vulgaris*) have been the criteria of a positive response, the time required for its production reaching the low level of less than three hours in the last of these tests.

All the above tests detect chorionic gonadotrophin, the action of which, as previously stated, is mainly luteinizing; they will not detect the gonadotrophin excreted in the urine of males and of non-pregnant women, which has a follicle-stimulating action. For this purpose criteria such as the increase in ovarian weight, the causation of vaginal opening or the production of vaginal cornification, all in immature rats or mice, can be used. It must, however, be emphasized that since chorionic gonadotrophin will also produce these effects, it is technically a most difficult (or even impossible) procedure to assay follicle-stimulating hormone in the presence of considerable amounts of chorionic gonadotrophin or other mainly luteinizing

hormone. For the quantitative assay of luteinizing gonadotrophin, criteria such as the increase in ovarian and uterine weight in the immature female rat or the increase in weight of the prostate and seminal vesicles of the immature male rat may be used. An interesting method involving the use of oestrogenized male cocks (Nalbandov and Baum, 1948) has been evolved recently, and by this means the presence of both follicle-stimulating and luteinizing activity can be differentiated, although not differentially assayed.

Except when the gonadotrophin is present in particularly large amounts, as in pregnancy and in the presence of certain testicular tumours, resort to methods of extracting and concentrating the excreted hormone is necessary. Twenty-four hour urine collections must be made and the treatment may then follow one of two main lines: the gonadotrophin may be precipitated by means of alcohol, tannic acid or benzoic acid and then further prepared so as to be suitable for injection into the test animals in graded doses; or the urine may be passed through a large ultrafilter, the protein constituents (including the gonadotrophins) being retained on the collodion membrane, which is removed and dissolved in an acetone-ether mixture from which the active material is recovered by centrifugation. Provided the apparatus is available, the latter is by far the more convenient of the two procedures.

CLINICAL VALUE OF GONADOTROPHIN ASSAYS

The principal reason for referring in some detail to the technical side of gonadotrophin assays is to emphasize the fact that they are not to be undertaken too lightly, and to point out that whereas the crude qualitative tests, such as the Aschheim-Zondek, Friedman or male-toad test, are relatively simple matters, the quantitative assays are an entirely different proposition. It is therefore pertinent to inquire what value these procedures may have for the clinician, and particularly when qualitative methods no longer serve but must be supplemented by the more complicated quantitative assays. With *the diagnosis of pregnancy* we need scarcely concern ourselves; highly accurate results are obtained from all the qualitative procedures in common use. The major *complications of pregnancy* associated with altered gonadotrophin excretion may similarly be dealt with in summary fashion: hydatidiform mole and chorio-epithelioma are usually associated with exaggerated outputs of chorionic gonadotrophin, so that the Friedman test is generally (but *not* always) positive in dilutions of 1 in 100 or more. What is sometimes forgotten is that the natural gonadotrophin peak (reached about the tenth week of gestation) and the increase of gonadotrophin excretion in multiple pregnancies may also give a positive Friedman test in high dilutions and so enhance the erroneous suspicion of hydatidiform mole, if other suggestive signs and symptoms are present. A case for quantitative chorionic gonadotrophin assays might be made out on the basis of the claims put forward by the Smiths (1948) that the gonadotrophin excretion is increased in patients with late toxæmia of pregnancy, and that this increase has a prognostic

significance; these findings, however, are neither generally accepted nor have they been confirmed, so that the matter is still of theoretical rather than of practical clinical importance.

It has long been known that certain *testicular tumours* may be associated with high outputs of urinary gonadotrophins, and attempts have been made to use hormone assays for diagnostic and prognostic purposes in these cases. A review of this subject has been given by Francis (1945-46) and the generally confused ideas which prevail have been pointed out. This confusion arises from the fact, as demonstrated by Hamburger *et al.* (1936), that two types of hormone may be involved: follicle-stimulating hormone produced by the patient's pituitary, and gonadotrophin of the chorionic variety arising from the tumour. The follicle-stimulating hormone may be present in normal amounts only, or in increased amount if normal testicular secretion of androgens is in abeyance, the increase then being comparable with that found in eunuchoids (*see* p. 433) and of the same significance; these findings may be present with seminomas, so that the Friedman test would be negative although, in the second of the two possibilities, the Aschheim-Zondek test might give a so-called reaction 1, consisting merely of

TABLE 2
GONADOTROPHIN EXCRETION IN TUMOUR CASES

Type of tumour	Urinary gonadotrophin		Friedman test
	F.S.H. (from pituitary)	Chorionic type (from tumour)	
Teratoma—adult type	Normal or increased	—	Negative
Teratoma—embryonal type	Normal or increased	Present in some cases	Positive or negative
Seminoma	Normal or increased	—	Negative
Chorio-epithelioma	Normal or increased	Present in nearly all cases	Positive
Embryonal carcinoma	Normal or increased	Present in some cases	Positive or negative

follicular ripening and quite distinct from a true positive response. It must be emphasized that the tumour itself in these cases is producing no gonadotrophin. On the other hand, chorio-epitheliomas and some embryonal carcinomas and teratomas of embryonal type secrete gonadotrophin of the chorionic variety, so that in these cases positive Friedman or Aschheim-Zondek tests are obtained, sometimes in exceedingly high dilution. A positive qualitative test therefore in a case of testicular tumour confines the diagnosis to one of these three types, and it cannot be said that quantitative assays yield any further information either of diagnostic or of prognostic value. Rarely, malignant tumours not of testicular origin may produce large amounts of gonadotrophin; cases of mediastinal chorio-epithelioma and two

cases of adrenocortical carcinoma (McFadzean, 1946; Chambers, 1949) have been reported as showing these properties, and from the fact that gynæcomastia also occurs in some of these cases, it is possible that the tumours produce œstrogens also. In table 2 the broad facts relating to gonadotrophin excretion in tumour cases are summarized.

Quantitative gonadotrophin assays have a diagnostic value in cases of *hypogonadism*, which may be primary, when the defect lies in the gonad itself, or secondary, when the condition is due to a deficiency of gonadotrophin. In primary hypogonadism the eunuchoid state is associated with an *increased* excretion of gonadotrophin, and such a finding would make therapy with gonadotrophins completely irrational; the functional inadequacy of the gonad must be accepted and, if necessary, replacement therapy with androgens (or œstrogens in the female) may be used in an attempt to produce normal psychic and somatic development. Increased gonadotrophin excretion is also found at the climacteric, and in both these states the explanation is that normally the gonadal secretions exert an inhibitory influence on the anterior pituitary; when they are absent or reduced the pituitary becomes correspondingly overactive. In secondary hypogonadism, gonadotrophin assays reveal a decreased excretion, and in these cases therapy with gonadotrophins is a rational procedure and may even be expected to have some chance of making the subject fertile.

A final word under the heading of gonadotrophin assays may be said concerning the interesting syndrome first described by Klinefelter, Reifenstein and Albright (1942). This consists of aspermia with hyalinization of the seminiferous tubules but without destruction of the interstitial cells of the testis, gynæcomastia, and an increased output of urinary gonadotrophin (of follicle-stimulating type, so not detectable by the Aschheim-Zondek or Friedman test). Heller and Nelson (1945) subsequently showed that gynæcomastia was not an essential part of the syndrome, that the degree of representation of the interstitial cells was variable and, curiously, that gynæcomastia occurred only in the cases with evidence of more fully active interstitial cells, being absent from patients with eunuchoid features.

THERAPY WITH GONADOTROPHINS

The clinician will conclude from what has already been said that gonadotrophin assays are not likely to prove of outstanding value to him other than in exceptional circumstances; he must now accept the further disappointment that therapy with gonadotrophins can in no way be considered as a panacea. There are various reasons for this: in the first place, as already mentioned, no satisfactory preparation of pituitary gonadotrophin is yet generally available, so that we have to rely mainly on the somewhat atypical chorionic and equine gonadotrophins for therapeutic purposes; in the second, the protein nature of the gonadotrophin may result in the production of antibodies when therapy is prolonged, and these antibodies may

be effective not only against the injected gonadotrophin but also against the patient's endogenous pituitary gonadotrophin; and in the third place, the use of gonadotrophins is still largely experimental so that rigid therapeutic schedules cannot generally be detailed. The remainder of this article will therefore consist of a survey of the field in which gonadotrophin therapy may have a value, real or imagined, together with some suggestions regarding dosage.

In the Male

Delayed puberty.—Treatment with chorionic gonadotrophin may be of value in some cases of delayed puberty; in general, treatment should not be started too early, and certainly not before the fifteenth year. Many of these patients undergo a normal puberty if left alone, and the risks of psychological upset that may follow the inevitable direction of the patient's attention to his abnormality through hormone therapy must be weighed against those of leaving the condition untreated. Dosage may be of the order of 500 I.U. intramuscularly once weekly, for ten weeks, the course being repeated once or twice after two to three months' intervals. If no response has followed the first course, the dosage may be increased to two or three times weekly in the second course.

Undescended testicle.—Much has been written on this subject (for a comprehensive review see Bishop, 1945), and divergent views exist as to whether or no gonadotrophins have any place in its treatment. Certainly for ectopia they can do nothing and surgery is the only form of treatment available. It is argued by the antagonists of hormone therapy that this succeeds only in cases wherein spontaneous descent would have occurred anyway. This form of argument is, of course, unanswerable, but the important fact remains that if the testicles do not descend before puberty the likelihood of their being spermatogenetically inadequate is very great, even though they descend spontaneously later. It seems reasonable therefore to make use of chorionic gonadotrophin, not later than at the age of twelve years, in all cases of inguinal (or canalicular) testicles, one or two courses of the types described above usually being sufficient. If this treatment fails, the patient *automatically* becomes a candidate for surgery and this will be facilitated by the previous treatment, in so far as it will have promoted growth of the spermatic cord.

Hypogonadism.—As previously mentioned, gonadotrophin therapy can be expected to have a value only in cases of secondary hypogonadism (with decreased gonadotrophin excretion). In these cases, courses of chorionic gonadotrophin will induce secretory activity in the interstitial cells with corresponding development of the accessory genital organs and secondary sexual characters. Supplementation with androgens (preferably by implantation of testosterone) is generally advisable. The subsequent concomitant use of equine gonadotrophin may lead to spermatogenesis in some cases.

It would be well to point out that before equine gonadotrophin is used,

skin testing should be the routine, to avoid reactions which are sometimes severe. An intradermal injection is made of 0.1 ml. of the solution to be used; if this is followed by more than trivial erythema, desensitization should be attempted or, perhaps better, the use of the gonadotrophin abandoned. These precautions are not necessary with chorionic gonadotrophin, which seldom produces reactions of any consequence.

Sterility.—Much use has been made of gonadotrophin therapy for male sterility, but on the whole the results have been most disappointing. This is because it is seldom if ever that the three criteria necessary for even the theoretical prospect of success are fulfilled. These criteria are: (1) the damage to the seminiferous epithelium must not be too great to prevent its responding to a potent gonadotrophin; (2) there must not be an increase in the patient's gonadotrophin excretion; (3) the gonadotrophin must be a potent follicle-stimulating preparation. Even when these requirements are met the development of anti-gonadotrophins limits or negatives the effectiveness of the treatment (Jungck *et al.*, 1949).

In the Female

Delayed puberty.—Theoretically, the use of gonadotrophins would be indicated when delayed puberty is associated with a decreased gonadotrophin excretion, i.e., due to deficiency of anterior pituitary function. In practice, however, it is seldom that such treatment would be used; substitution therapy with oestrogens would be chosen, if only because of the inconvenience of repeated injections of the gonadotrophin, to say nothing of the increasing likelihood of reactions and the development of anti-gonadotrophins with each successive course of equine gonadotrophin.

Induction of ovulation.—The use of gonadotrophins for this purpose seems logical, although since we are still ignorant of the exact mechanism involved in the induction of ovulation, it is not surprising that success is relatively uncommon. The "one-two cyclic" method of Hamblen (1947) may be tried: it consists in giving ten daily intramuscular injections, each of 400 I.U. of equine gonadotrophin (starting on the fifth day of the cycle if the patient is having anovular cycles), followed immediately by ten daily intramuscular injections, each of 500 I.U. of chorionic gonadotrophin. If the endometrial biopsy taken at the start of the succeeding bleeding episode fails to show secretory changes, treatment is given again, after the lapse of one cycle, in the same manner as before but with the dosage doubled. If the biopsy is still proliferative at the start of the bleeding episode which follows, the ovaries are judged to be refractory and further treatment is contraindicated.

Prolonged and excessive uterine bleeding.—The use of chorionic gonadotrophin has been advocated in the treatment of prolonged and excessive uterine bleeding on the grounds that progesterone deficiency exists in this condition and that the gonadotrophin would stimulate the production of progesterone. Since progesterone deficiency is not necessarily the most

fundamental functional derangement in this condition (and does not exist at all in most cases of *regular* menorrhagia), whilst the effectiveness of chorionic gonadotrophin in stimulating secretion of progesterone is open to doubt, it cannot be said that the rationale is altogether sound. It is probable that the success which sometimes follows this treatment (usually prescribed in what is almost homœopathic dosage) is to be ascribed to the psychotherapeutic aspect of the repeated injections rather than to the action of the hormone itself.

Threatened and habitual abortion.—The belief is common that threatened and habitual abortion are due to deficiency of progesterone, for which reason chorionic gonadotrophin has been advocated in treatment. It is true that *some* cases have such an etiology, and for these, supplementation with progesterone is a rational procedure; administration of chorionic gonadotrophin is *not*, since the patient is already excreting far larger amounts than the ordinary dosage schedules would supply. If this natural gonadotrophin plethora is not present, i.e., if the Friedman test is negative, then the embryo is no longer viable and the abortion has already become inevitable or "missed".

CONCLUSION

The clinical status of gonadotrophins must be judged on the basis of the help they afford the practitioner, either as diagnostic or therapeutic aids. Except for the crude qualitative tests for chorionic gonadotrophin, such as the Aschheim-Zondek, Friedman and similar tests, assays have a limited scope, partly by reason of the difficulty of performing them properly and partly by reason of the rarity of the conditions for which they may provide diagnostic assistance. In therapy too, the position is disappointing; gonadotrophins have to be given by repeated intramuscular injection, they may cause reactions and lead to the development of anti-gonadotrophins, and because their use is still largely experimental, successes from gonadotrophin therapy are not frequent.

References

- Aschheim, S., and Zondek, B. (1928): *Klin. Wschr.*, 7, 8.
 Bishop, P. M. F. (1945): *Guy's Hosp. Rep.*, 94, 12.
 Chambers, W. L. (1949): *J. clin. Endocrinol.*, 9, 451.
 Francis, R. S. (1945-46): *Brit. J. Surg.*, 33, 173.
 Friedman, M. H. (1929): *Amer. J. Physiol.*, 90, 617.
 Gordon, I. (1949): *Lancet*, i, 807.
 Hamblen, E. C. (1947): "Endocrinology of Woman," Springfield, Illinois.
 Hamburger, C., Bang, F., and Nielsen, J. (1936): *Acta. path. microbiol. scand.*, 13, 75.
 Heller, C. G., and Nelson, W. O. (1945): *J. clin. Endocrinol.*, 5, 1.
 Jungck, E. C., *et al.* (1949): *Ibid.*, 9, 355.
 Klinefelter, H. F., Reifstein, E. C., and Albright, F. (1942): *Ibid.*, 2, 615.
 McFadzean, A. J. S. (1946): *Lancet*, ii, 940.
 Nalbandov, A. V., and Baum, G. J. (1948): *Endocrinology*, 43, 371.
 Smith, G. van S., and Smith, O. W. (1948): *Physiol. Rev.*, 28, 1.

HORMONE IMPLANTATION THERAPY

By P. M. F. BISHOP, D.M.

Endocrinologist, Guy's Hospital, and Chelsea Hospital for Women; Senior Lecturer in Endocrinology, Department of Obstetrics and Gynecology, British Postgraduate Medical School.

WHEN the sex hormones began to be isolated in purified form, from 1929 onwards, an intensive study of methods for increasing their activity and prolonging their effectiveness naturally followed, for they were, at this time, laborious to produce, difficult to come by, and expensive to employ. A variety of methods, such as addition of an "x-substance", or of pure fatty acids to the solution injected, esterification of the hormone, or simply increasing the volume of oil in which the hormone was injected, were investigated and reported upon. It was during the course of this last investigation that Deanesly and Parkes (1937) found to their surprise that increase in volume of the oily medium beyond a certain point actually decreased the effectiveness of the androgenic compounds, androstenediol and *trans*-androstenediol. Both these substances are very sparingly soluble in oil, and solutions more concentrated than 1 mg. per ml. crystallize out. Injection of this "crystal mush" was found to be more effective than the oil solution. It therefore occurred to these workers to study the effect of implanting solid crystalline tablets of the hormone subcutaneously. This method greatly increased the effectiveness and duration of activity of the hormone.

The prolongation of activity and increased effectiveness were properties of considerable value to workers studying such a variety of effects of sex hormones as inhibition of the growth-promoting activity of the pituitary (Deanesly, 1939; Noble, 1939), production of carcinoma in susceptible mice (Twombly, 1939), and of myomas in rats (Lipschütz and Vargas, 1939), and the metabolism of sex hormones following intra-splenic implants (Biskind and Mark, 1939).

Clinicians were not slow in appreciating the potential value of this new method of administration. Thus a 14 mg. pellet of *œstrone* was implanted subcutaneously in a castrated woman of twenty-two, relieving her menopausal symptoms for five weeks (Bishop, 1938). Foss (1939) employed the method in treating 15 women suffering from post-menopausal dermatoses, and Salmon *et al.* (1939) used *œstradiol benzoate* implants in the treatment of menopausal women. Hormone pellet implantation is now a well-established therapeutic technique.

THE MECHANICS OF HORMONE ABSORPTION FROM IMPLANTED PELLETS

(1) *Methods of preparing the pellet*

Pellets were originally made by *compressing* the hormone crystals in a

hand tablet-making press. Sufficient pressure was used to ensure that the pellet did not flake or disintegrate in handling. Satisfactory commercial manufacture of compressed pellets on a large scale is more easily ensured if the hormone is diluted with lactose, with a small quantity of stearic acid as a lubricant (Parkes, 1946).

Pellets are also prepared by melting the crystals of the hormone in a hollow metal cylinder and subsequently allowing them to solidify by cooling (Shimkin and White, 1941). These are referred to as *fused* or *cast* pellets. Although most of the steroid hormones used in clinical practice, for instance oestradiol, testosterone, progesterone and deoxycorticosterone acetate, can be prepared in the form of fused pellets, certain compounds, such as stilboestrol, are satisfactorily prepared only as compressed pellets.

(2) *Phenomena observed during absorption*

Encapsulation.—Whenever a pellet is implanted a fibrous tissue capsule forms around it. These capsules may be tough and avascular, and they may consequently retard or even completely prevent further absorption. This may account for the clinical observation that in some cases the effectiveness of the hormone ceases rather suddenly and prematurely, although the pellet may be removed and found to be of substantial size.

"Ghost" formation.—Folley (1942) observed that pellets which had been removed after implantation did not dissolve when treated with ether to extract the hormone. A skeleton or "ghost" remains, approximately of the same shape and size as the pellet. This ghost appears on chemical analysis to be a scleroprotein. Its formation is due to a surface reaction between the material of the pellet and protein in solution in the tissue fluid bathing it (Folley, 1944). Ghost formation is more prominent in compressed pellets, because the method of preparation leaves interstices throughout the structure of the pellet, where this surface reaction may take place. Ghosts, however, have been shown to be present after implantation of fused pellets, although they are confined to the surface of the pellet (Deanesly and Parkes, 1943). When the hormone has been "diluted" with lactose, this substance is rapidly dissolved after implantation, leaving well-marked interstitial spaces in which this surface reaction will subsequently take place. Ghost formation must be taken into account when accurate measurements are made of the amount of hormone absorbed in a given period of time, for the weight of the ghost may be considerable. On the other hand the ghost does not affect the rate of absorption of the hormone to any great extent (Cowie and Folley, 1946).

The "labile" component.—Folley (1944) found that during the first few days after implantation, absorption was much more rapid than in the subsequent stages. He showed that this was due neither to encapsulation nor to ghost formation, and postulated that the pellet easily loses a "labile" component when brought in contact with body fluids, and that the surface which remains after the "labile" component is lost is many times more

insoluble than the original surface of the pellet. This rapid initial absorption is not reflected in an enhanced hormone effect, and indeed it is not usual to find any clinical improvement as the result of hormone implantation for the first week or fortnight.

Extrusion.—It is an undoubted clinical observation that certain hormone pellets tend to “extrude” more readily than others. This phenomenon seems to apply particularly to human tissues, for it is not mentioned in the reports of pellet implantation in experimental animals. It is obvious that the procedure of implantation consists in introducing a foreign body into the tissues, and although the pellet has been carefully sterilized, every precaution should be taken to see that it is implanted under aseptic conditions. Unless it is, there is danger of local suppuration and abscess formation, in the process of which the pellets will fall out. “Extrusion”, however, is an entirely different reaction. It often occurs long after the incision has healed by first intention, and indeed sometimes the pellet is extruded not through the incision but through a separate hole it makes for itself in the adjacent skin. As extrusion is apt to occur especially when pellets are very superficially implanted under the skin, care should be taken, in implanting pellets which are known to be liable to extrude, to ensure that they are deeply placed. Progesterone is especially likely to extrude, and should therefore always be placed deeply. Testosterone propionate also has a tendency to extrude, and for this reason the free hormone, testosterone, is usually employed. Extrusion is seldom encountered when œstradiol, stilbœstrol, testosterone and deoxycorticosterone acetate pellets are implanted.

FACTORS AFFECTING THE ABSORPTION RATE

Absorption remains remarkably constant for any particular hormone and any particular size and shape of pellet. On general principles it might be supposed that absorption would be more rapid if the pellet were implanted into a host who showed signs of deficiency of the hormone employed: this is not the case. Neither does the site of implantation appreciably affect the rate of absorption. As esterification prolongs the duration of effect of injected hormones it might be considered that it would do the same for implanted hormones: there seems to be no uniform pattern to support this theory. Hormone pellets “diluted” with lactose do not lead to a more rapid absorption of the hormone. Indeed, the only factors to be considered are the size and shape of the pellets, and the nature of the hormone.

Surface area of the pellet.—Bishop and Folley (1944) studied the absorption rate of a large number of pellets of compressed and fused hormones of different types. A theoretical curve was constructed to represent the absorption in the human of fused pellets of approximately 100 mg. of testosterone, and of known radius and height, assuming that the only factor affecting absorption rate would be the diminishing surface area of the pellet. Pellets, previously accurately weighed, were implanted into a series of patients, and removed at specified intervals after implantation, re-

weighed and corrected for ghost formation, which was negligible because the pellets were fused. A curve was constructed showing the actual rate of absorption. This curve corresponded satisfactorily with the theoretically predicted curve. Thus for fused pellets of testosterone the rate of absorption depends almost entirely upon the surface area of the pellet and the time since it has been implanted.

Rate of absorption of various hormones.—The rate of absorption depends upon the surface area and therefore the size and shape of the pellet, and the nature of the hormones. It is clear that the smaller the pellet the greater is the relative extent of its surface area. There is therefore an actual disadvantage in implanting pellets exceeding a certain weight. Probably the most convenient weight to handle and the one which yields the most efficient surface area, is 100 mg., and if one wishes to implant a total dose of 600 mg. of testosterone, one would probably implant it in the form of six 100 mg. pellets, rather than as one 600 mg. pellet.

Much has been written concerning the specific absorption rate of different hormones and other substances. Some of this work has been carried out on animals, and does not necessarily apply to human tissues. For instance, Forbes (1943) investigated the absorption rate of different hormone pellets in rats, and found that testosterone was absorbed considerably more rapidly than stilbæstrol. In man, however, stilbæstrol is absorbed slightly more rapidly than testosterone. Deanesly, Folley and Parkes (1946) found that œstriol triacetate and certain non-hormonal compounds, such as silica and sulphanilamide, disappeared rapidly, whereas ethisterone, stilbæstrol dibenzoate and œstradiol dibenzoate were practically not absorbed at all. Parkes (1942) and others have investigated the fate of pellets of certain protein hormones, using cholesterol or sulphanilamide as excipients. Thyroxine is practically not absorbed at all. Adrenaline has a fair duration of effectiveness, and insulin is usually lethal to the animal. Vargas (1949), however, claims satisfactory results in the treatment of diabetes mellitus from implantation of pellets of protamine zinc insulin mixed with cholesterol. In general, however, it would seem unsuitable to use the implantation method in diabetes in which the blood sugar level is subject to such fluctuations, and when there is therefore danger of serious hypoglycæmic attacks if a constant dose of insulin is being maintained and cannot be altered. Implantation of chorionic, and horse and sheep pituitary, gonadotrophins mixed with 90 per cent. of cholesterol, markedly increased the effectiveness of the hormone which gave a uniform absorption over short periods (about a week). In the human subject, the absorption rate of different hormones has been studied. Thorn and Firor (1940) found that pellets of deoxycorticosterone acetate remained effective in cases of Addison's disease for nine to twelve months. Greenblatt and Hair (1945) showed that the absorption rate of progesterone was about 20 per cent. per month. Foss (1942) examined the absorption rate of progesterone, testosterone, testosterone propionate, œstradiol and œstrone, and found the rate to

diminish in that order. Bishop and Folley (1944) showed that 100 mg. fused pellets of testosterone were completely absorbed in 220 days.

Summarizing the reports of other workers and my own experience the following approximate figures may be tentatively put forward.

Hormone	Approximate duration of effectiveness of 100 mg. pellet
Stilbæstrol	4 to 5 months
Testosterone	5 to 7 months
Deoxycorticosterone acetate	8 to 12 months
Estradiol	12 to 18 months

Progesterone is not included in this list because I have never been able to place it sufficiently superficially to find and remove it subsequently without the very great likelihood of its extruding.

THE TECHNIQUE OF HORMONE PELLET IMPLANTATION

Various techniques have been evolved by different workers, and there is perhaps a tendency to suggest that pellet implantation is a procedure which requires special technical dexterity not easily acquired by the practitioner. This is by no means true. The problem is quite simple. It is required to lodge somewhere beneath the skin one or more sterilized foreign bodies in such a way that the wound heals by first intention, and with the minimum of discomfort to the patient. It is well to realize that the pellets are foreign bodies and therefore to take every possible precaution that they are implanted aseptically. It is therefore wise—indeed, in my opinion, essential—to conduct this minor operation with full surgical technique in an operating theatre. A sterile gown, cap, mask and gloves should be worn, and the patient should be carefully towelled up. Various sites have been chosen for the implantation, such as the forearm, where a permanently disfiguring scar is produced, the subscapular region of the back, where the skin is thick and vascular, the abdominal wall, either in the midline below the umbilicus, or at the outer border of the rectus muscle, the region superficial to the inguinal canal, and the region of the hip. I have finally selected the latter. Within the triangle formed by a line drawn horizontally backwards for three inches from the anterior superior spine of the ilium, and a line dropped vertically for three inches from the highest point of the iliac crest, there is a convenient area which is relatively avascular, amply supplied by muscle, should deep implantation be indicated, and undisturbed by any movement of the leg in relation to the trunk. The implantation is carried out under local anæsthesia, consisting of 1 per cent. procaine, with the addition of 2 minims (0.12 ml.) of adrenaline to the ounce (28.5 ml.). The local anæsthetic is injected from a Labat's syringe with an eccentric nozzle so that the needle lies horizontal to the skin and permits easy infiltration of the superficial layers. The needle should be of fine bore, and no longer than two inches (a no. 2 needle). A superficial wheal of about the size of half-a-crown should be made. A Bard-Parker no. 3 scalpel with a small, flat blade (no. 15 blade) should be used for the incision, which should extend for one-half to two

inches according to the number of pellets to be implanted, and parallel to the iliac crest. The incision should penetrate the skin and incise the superficial subcutaneous layer. Occasionally a superficial vessel is severed and the bleeding should promptly be controlled with a small Dunhill's artery forceps. Holding the lip of the incision with a pair of fine-toothed dissecting forceps, blunt dissection with a pair of round-pointed iridectomy scissors

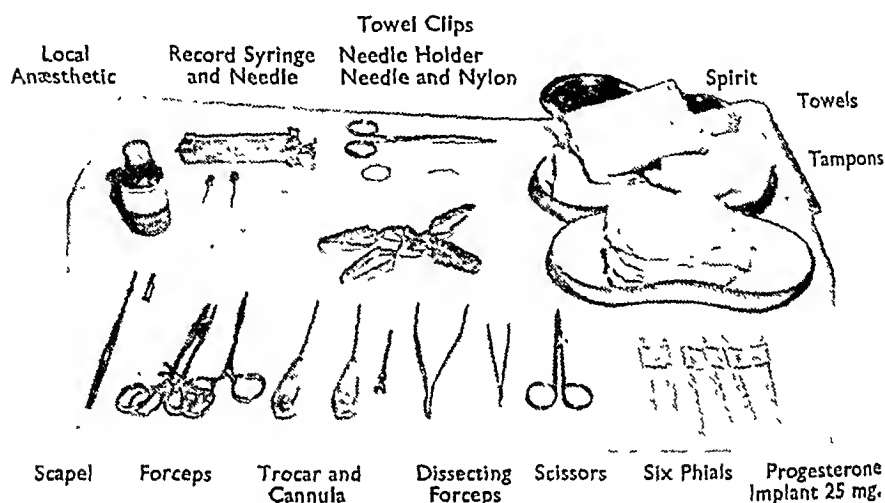


FIG. 1.—TRAY PREPARED FOR HORMONE IMPLANTATION.

is then made between the skin and the fatty subcutaneous layer. A pocket is thus made first on one side and then on the other of the incision. The pocket should extend at least two inches from the incision and should be made broad enough to accommodate the requisite number of pellets to be implanted. Thus if six 100 mg. pellets of testosterone are to be implanted, 3 will be lodged in the pocket above the incision and 3 in the pocket below it. If care is taken to make the pocket exactly at the level of contact between skin and subcutaneous tissue practically no bleeding will be produced. If oozing does occur, it must be controlled before the tablets are implanted. The tablets should finally lie in the pockets, sufficiently remote from the incision so that they cannot be seen when the skin edges are brought together with 1, 2 or 3 small nylon stitches. The wound should be covered with a very small dry dressing of sterile gauze and a small oval-shaped piece of Elastoplast the size of a crown piece. Instructions are given to the patient to keep the dressing dry (i.e. not to have a bath), and to have the stitches removed in ten days and to continue to wear a dressing for another four days.

Deep implantation.—In the case of progesterone it is necessary to implant the pellets deeply. For this purpose a trocar and cannula are used. I have the pellets made in the form of thin long cylinders weighing 25 mg. each, so

that the cannula need only be of fine bore and trauma to the tissues is minimized. Using the same site of implantation a short incision is made through the skin and deep fascia. The knife is then stabbed into the underlying muscle to make a track along which the cannula can be subsequently directed. Care, however, should be taken, especially in a thin patient, to avoid touching the periosteum of the iliac bone, for that may cause pain. It is desirable to make a separate track for each pellet, but this does not always necessitate a separate stab: the cannula can often be manipulated *in situ*, so that the next pellet is lodged at some distance from the previous one. Each pellet is placed in the mouth of the cannula and gently pressed into position by the blunt-ended trocar.

Some workers use a trocar and cannula even for superficial implantation. I prefer to visualize the floor of the subcutaneous pocket, to make sure there is no oozing before the incision is closed; otherwise a bruise or even a quite severe hæmatoma may develop, which will not only be painful, but may lead to expulsion of the pellets.

Removal of pellets.—Should it ever become necessary to remove a pellet it is as well to feel for it and mark its position with some sterile dye, such as Bonney's paint, before injecting the local anæsthetic, for the wheal will mask its position. The scar of the previous incision should be removed by making an elliptical incision.

INDICATIONS FOR HORMONE IMPLANTATION THERAPY

This method of administration is indicated in cases in which it is desirable to obtain a concentrated and constant effect over a long period of time.

Estrogens.—Implantation therapy should not be employed in women before the menopause, as it will give rise to flooding from a metropathic type of endometrium. The only exception to this rule is in cases of pseudo-hermaphroditism or ovarian agenesis in which no ovarian activity is demonstrable, and in which it is desirable to induce such secondary sexual characters as development of the breasts; three 100 mg. pellets of stilbæstrol or œstradiol shou'd then be used. Small doses of œstrogen, e.g. 50 mg. of œstradiol, may be given to control the menopausal symptoms of patients who have undergone a bilateral oöphorectomy, especially if the uterus has also been removed. Œstrogens have for some time been employed in large doses for the treatment of carcinoma of the breast, in post-menopausal women, and for carcinoma of the prostate. Implantation would seem to be an ideal mode of administration, and doses up to three 100 mg. pellets of stilbæstrol or œstradiol are probably considerably more effective than oral or parenteral treatment.

Progesterone.—Progesterone implants are used in cases of habitual abortion, in which it is considered that there is inadequate secretion of this hormone. The pellets should be implanted deeply, and six 25 mg. pellets seem to be an effective dose.

inches according to the number of pellets to be implanted, and parallel to the iliac crest. The incision should penetrate the skin and incise the superficial subcutaneous layer. Occasionally a superficial vessel is severed and the bleeding should promptly be controlled with a small Dunhill's artery forceps. Holding the lip of the incision with a pair of fine-toothed dissecting forceps, blunt dissection with a pair of round-pointed iridectomy scissors

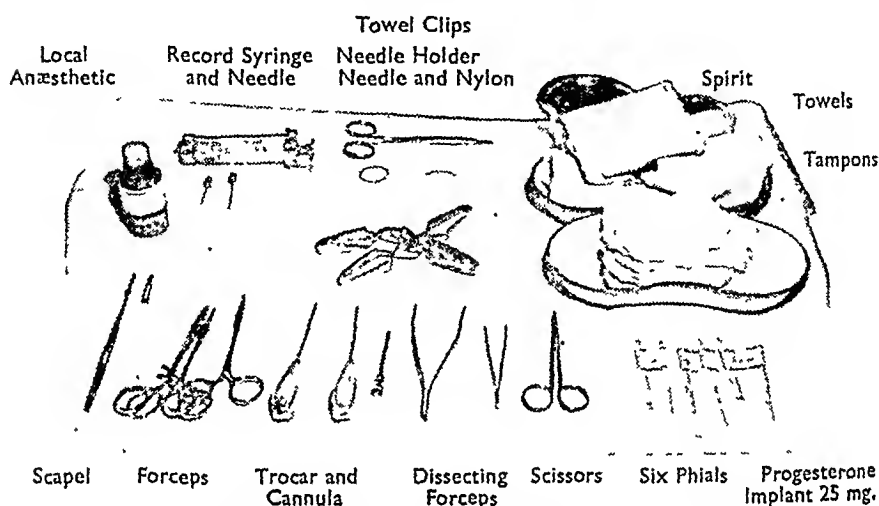


FIG. 1.—TRAY PREPARED FOR HORMONE IMPLANTATION.

is then made between the skin and the fatty subcutaneous layer. A pocket is thus made first on one side and then on the other of the incision. The pocket should extend at least two inches from the incision and should be made broad enough to accommodate the requisite number of pellets to be implanted. Thus if six 100 mg. pellets of testosterone are to be implanted, 3 will be lodged in the pocket above the incision and 3 in the pocket below it. If care is taken to make the pocket exactly at the level of contact between skin and subcutaneous tissue practically no bleeding will be produced. If oozing does occur, it must be controlled before the tablets are implanted. The tablets should finally lie in the pockets, sufficiently remote from the incision so that they cannot be seen when the skin edges are brought together with 1, 2 or 3 small nylon stitches. The wound should be covered with a very small dry dressing of sterile gauze and a small oval-shaped piece of Elastoplast the size of a crown piece. Instructions are given to the patient to keep the dressing dry (i.e. not to have a bath), and to have the stitches removed in ten days and to continue to wear a dressing for another four days.

Deep implantation.—In the case of progesterone it is necessary to implant the pellets deeply. For this purpose a trocar and cannula are used. I have the pellets made in the form of thin long cylinders weighing 25 mg. each, so

that the cannula need only be of fine bore and trauma to the tissues is minimized. Using the same site of implantation a short incision is made through the skin and deep fascia. The knife is then stabbed into the underlying muscle to make a track along which the cannula can be subsequently directed. Care, however, should be taken, especially in a thin patient, to avoid touching the periosteum of the iliac bone, for that may cause pain. It is desirable to make a separate track for each pellet, but this does not always necessitate a separate stab: the cannula can often be manipulated *in situ*, so that the next pellet is lodged at some distance from the previous one. Each pellet is placed in the mouth of the cannula and gently pressed into position by the blunt-ended trocar.

Some workers use a trocar and cannula even for superficial implantation. I prefer to visualize the floor of the subcutaneous pocket, to make sure there is no oozing before the incision is closed; otherwise a bruise or even a quite severe hæmatoma may develop, which will not only be painful, but may lead to expulsion of the pellets.

Removal of pellets.—Should it ever become necessary to remove a pellet it is as well to feel for it and mark its position with some sterile dye, such as Bonney's paint, before injecting the local anæsthetic, for the wheal will mask its position. The scar of the previous incision should be removed by making an elliptical incision.

INDICATIONS FOR HORMONE IMPLANTATION THERAPY

This method of administration is indicated in cases in which it is desirable to obtain a concentrated and constant effect over a long period of time.

Œstrogens.—Implantation therapy should not be employed in women before the menopause, as it will give rise to flooding from a metropathic type of endometrium. The only exception to this rule is in cases of pseudohermaphroditism or ovarian agenesis in which no ovarian activity is demonstrable, and in which it is desirable to induce such secondary sexual characters as development of the breasts; three 100 mg. pellets of stilbæstrol or œstradiol should then be used. Small doses of œstrogen, e.g. 50 mg. of œstradiol, may be given to control the menopausal symptoms of patients who have undergone a bilateral oöphorectomy, especially if the uterus has also been removed. Œstrogens have for some time been employed in large doses for the treatment of carcinoma of the breast, in post-menopausal women, and for carcinoma of the prostate. Implantation would seem to be an ideal mode of administration, and doses up to three 100 mg. pellets of stilbæstrol or œstradiol are probably considerably more effective than oral or parenteral treatment.

Progesterone.—Progesterone implants are used in cases of habitual abortion, in which it is considered that there is inadequate secretion of this hormone. The pellets should be implanted deeply, and six 25 mg. pellets seem to be an effective dose.

that the cannula need only be of fine bore and trauma to the tissues is minimized. Using the same site of implantation a short incision is made through the skin and deep fascia. The knife is then stabbed into the underlying muscle to make a track along which the cannula can be subsequently directed. Care, however, should be taken, especially in a thin patient, to avoid touching the periosteum of the iliac bone, for that may cause pain. It is desirable to make a separate track for each pellet, but this does not always necessitate a separate stab: the cannula can often be manipulated *in situ*, so that the next pellet is lodged at some distance from the previous one. Each pellet is placed in the mouth of the cannula and gently pressed into position by the blunt-ended trocar.

Some workers use a trocar and cannula even for superficial implantation. I prefer to visualize the floor of the subcutaneous pocket, to make sure there is no oozing before the incision is closed; otherwise a bruise or even a quite severe hæmatoma may develop, which will not only be painful, but may lead to expulsion of the pellets.

Removal of pellets.—Should it ever become necessary to remove a pellet it is as well to feel for it and mark its position with some sterile dye, such as Bonney's paint, before injecting the local anæsthetic, for the wheal will mask its position. The scar of the previous incision should be removed by making an elliptical incision.

INDICATIONS FOR HORMONE IMPLANTATION THERAPY

This method of administration is indicated in cases in which it is desirable to obtain a concentrated and constant effect over a long period of time.

Œstrogens.—Implantation therapy should not be employed in women before the menopause, as it will give rise to flooding from a metropathic type of endometrium. The only exception to this rule is in cases of pseudo-hermaphroditism or ovarian agenesis in which no ovarian activity is demonstrable, and in which it is desirable to induce such secondary sexual characters as development of the breasts; three 100 mg. pellets of stilbœstrol or œstradiol should then be used. Small doses of œstrogen, e.g. 50 mg. of œstradiol, may be given to control the menopausal symptoms of patients who have undergone a bilateral oöphorectomy, especially if the uterus has also been removed. Œstrogens have for some time been employed in large doses for the treatment of carcinoma of the breast, in post-menopausal women, and for carcinoma of the prostate. Implantation would seem to be an ideal mode of administration, and doses up to three 100 mg. pellets of stilbœstrol or œstradiol are probably considerably more effective than oral or parenteral treatment.

Progesterone.—Progesterone implants are used in cases of habitual abortion, in which it is considered that there is inadequate secretion of this hormone. The pellets should be implanted deeply, and six 25 mg. pellets seem to be an effective dose.

Testosterone.—Implantation of testosterone pellets is primarily indicated in cases of eunuchoidism due to failure of testicular development. Six 100 mg. pellets are usually adequate and should be repeated every six months. Adult males who have been castrated as the result of injury to the testicles or tuberculous epididymo-orchitis are satisfactorily treated by this method. Testosterone has a protein-anabolic effect. In cases of total pituitary failure, such as Simmonds's disease, the muscular atrophy which leads to true muscular weakness can be overcome by an implantation of four 100 mg. pellets of testosterone. Large doses of androgen are also being used in cases of carcinoma of the breast in pre-menopausal women, and eight to ten 100 mg. pellets should be implanted every six months. It should be emphasized that this treatment should be reserved for inoperable cases, and advice should be sought from a recognized authority before embarking upon it.

Deoxycorticosterone acetate.—Implantation of this hormone has for some time been employed in cases of Addison's disease. There has been a tendency to calculate too accurately the hormone requirement of any individual patient, without due regard to the increased effectiveness of the hormone when administered by implantation. It is probably safer to give a relatively small implant, such as two to four 100 mg. pellets as a basic dose, and cut down the supplementary salt intake proportionately. This treatment is rather specialized, and it is as well to seek the advice of a consultant who has considerable experience of the condition. Overdosage may lead to œdema, and sometimes to pulmonary œdema, which may not be easy to detect, but which may have serious, and even fatal, consequences.

References

- Bishop, P. M. F. (1938): *Brit. med. J.*, **i**, 939.
 —, and Folley, S. J. (1944): *Lancet*, **i**, 434.
 Biskind, G. R., and Mark, J. (1939): *Johns Hopk. Hosp. Bull.*, **65**, 212.
 Cowie, A. T., and Folley, S. J. (1946): *J. Endocrinol.*, **4**, 375.
 Deanesly, R. (1939): *Ibid.*, **1**, 36.
 —, Folley, S. J., and Parkes, A. S. (1946): *Ibid.*, **4**, 422.
 —, and Parkes, A. S. (1937): *Proc. Roy. Soc. B.*, **124**, 279.
 —, — (1943): *Lancet*, **ii**, 500.
 Folley, S. J. (1942): *Nature*, **150**, 403.
 — (1944): *Proc. Roy. Soc. B.*, **132**, 1944.
 Forbes, T. R. (1943): *Endocrinology*, **32**, 282.
 Foss, G. L. (1939): *J. Obst. Gynec. Brit. Emp.*, **46**, 271.
 — (1942): *J. Endocrinol.*, **3**, 107.
 Geist, S. H., Walter, R. I., and Salmon, U. J. (1940): *Proc. Soc. exp. Biol., N.Y.*, **43**, 712.
 Greenblatt, R. B., and Hair, L. Q. (1945): *J. Endocrinol.*, **5**, 38.
 Lipschütz, A., and Vargas, L. (1939): *Lancet*, **i**, 1313.
 Noble, R. L. (1939): *J. Endocrinol.*, **1**, 216.
 Parkes, A. S. (1942): *Ibid.*, **3**, 220.
 — (1946): *Ibid.*, **4**, 386.
 Salmon, U. J., Walker, R. I., and Geist, S. H. (1939): *Science*, **90**, 162.
 Shimkin, M. B., and White, J. (1941): *Endocrinology*, **29**, 1020.
 Thorn, G. W., and Firor, W. M. (1940): *J. Amer. med. Ass.*, **114**, 2517.
 Twombly, G. H. (1939): *Proc. Soc. exp. Biol., N.Y.*, **40**, 430.
 Vargas, L. (1949): *Lancet*, **i**, 598.

PAIN IN PERIPHERAL VASCULAR DISEASE

BY A. J. SLESSOR, M.V.O., F.R.C.S.

AND SIR JAMES LEARMONTH, K.C.V.O., C.B.E., CH.M., F.R.C.S.,
F.R.C.S.ED.

From the Department of Surgery, University of Edinburgh.

PAIN, the most common symptom of peripheral vascular disease, is due in almost every instance to ischæmia, so that this article is concerned primarily with obliterative arterial disease. Other disorders of the arterial tree, such as Raynaud's disease and diseases of the veins and lymphatics, cause discomfort rather than true pain, and are therefore excluded.

PAIN IN OBLITERATIVE ARTERITIS

The term obliterative arteritis includes two conditions: thromboangiitis obliterans and arteriosclerosis (including arteriosclerosis obliterans, Mönckeberg's sclerosis, and atheroma). Both conditions are much commoner in men than in women; thromboangiitis occurs almost exclusively in men under forty and arteriosclerosis mainly in men over fifty, whilst between these ages symptoms may be due to late onset of thromboangiitis or early onset of arteriosclerosis.

The etiology and pathology of the two conditions are different, but the macroscopic appearances of the arteries at the sites of occlusion are similar; there are changes in the vessel wall and partial or complete occlusion of the lumen. In both, complete occlusion results from thrombosis, the thrombus being later converted into fibrous tissue through which new channels may pass in an attempt to recanalize the artery. An artery may show complete occlusion, or only some narrowing, at one point; or over a long segment the lumen may be irregularly narrowed, or it may be completely obliterated. In thromboangiitis it is common to find several segments of complete occlusion separated by segments of apparently normal artery. It is important to appreciate that not only may the main arteries of a limb be involved, but also the smaller arteries which might take part in the collateral circulation, or bypass, around an obstruction. The result of the various degrees of obstruction is ischæmia of varying degree in the distal tissues, which may cause one or more of four types of pain: (1) intermittent claudication; (2) rest pain; (3) ischæmic neuritis; (4) pain of ulceration—gangrene.

INTERMITTENT CLAUDICATION

This is a symptom of muscle ischæmia, and because obliterative arteritis affects the vessels of the lower limb more often than those of the upper limb, intermittent claudication occurs mainly in the leg. The muscles of the calf are particularly affected, and the history is typical. The patient states

that, after walking a certain distance, he experiences a sense of fatigue in one or other calf; if he continues, this develops into true pain, which is cramp-like and tends to be most severe on the inner aspect of the calf; if he persists further, the pain increases until he is forced to stop and rest; after a short period the pain disappears completely. He may then resume his walk until he has covered the same distance, when the process is repeated. This distance is the "claudication distance", and it is almost constant for any one individual, between 20 yards and 800 yards or more. It is increased if he walks slowly or downhill, and reduced if he walks quickly or uphill; it is commonly shorter in cold weather. It is important to recognize that the pain is relieved by a short period of rest and without change of posture, two points which distinguish it from pain of non-vascular origin.

After the calf, the intrinsic muscles of the foot are those most often affected. The pain is brought on by walking, but it is less cramp-like than calf pain and it is often described as the sensation felt when "crossing pebbles barefoot"; this is because the ischæmia affects not one large muscle, but a number of small muscles which suffer short periods of claudication in turn, and so give rise to this "knobbly" pain. It is quickly relieved by rest. In advanced disease any muscle may claudicate, and pain on exercise has been described in the thigh, gluteal and lumbar muscles. Except in advanced thromboangiitis, it is rare in the upper extremity.

In most cases, the site of claudication indicates the approximate level of the arterial obstruction; if the foot alone claudicates, the obstruction is in the lower leg, whereas if the calf is affected, a popliteal or femoral occlusion will be suspected. In most cases, palpation of the pulses will confirm these suspicions, but occasionally claudication occurs in the calf when distal pulses are present. In this event, the arterial occlusions lie in the sural arteries which supply the two heads of gastrocnemius. These are end arteries, and collateral circulation is not available to meet the needs of exercise. Most muscles have alternative blood supplies, and are therefore less liable to suffer ischæmia, even when the main vessel of the limb is occluded; indeed, circulation within muscles is sometimes increased by occlusion of the main vessel to participate in the bypass, although the main collateral circulation develops in subcutaneous and named branches of the main vessel.

It remains to mention one other factor—arterial spasm—in the causation of ischæmic claudication. That spasm occurs in thromboangiitis is well established, and it is probably a factor in producing ischæmia in younger patients with arteriosclerosis. It is doubtful, however, if spasm ever causes intermittent claudication in the absence of organic arterial disease. In a small number of patients, distal pulses present at rest are temporarily abolished by exercise. This effect must be due to spasm; it is almost certain that these patients, who are usually in the early forties, have organic disease which cannot yet be identified, and they should be treated as patients with

early obliterative arteritis and observed over a period of years for further evidence of arterial occlusion.

By what mechanism does muscle ischæmia produce pain? Not oxygen lack, because venous blood from the lower limb of a patient with obliterative disease is better oxygenated than venous blood from a healthy lower limb. The exact cause of claudication is not known, but it is probably the accumulation of muscle metabolites produced during activity and extruded from the fibres to lie in the tissue spaces as relatively stable chemical compounds; in normal muscle these are destroyed or removed, but in ischæmic muscle their dispersal lags behind their production. That the pain stimulus is physico-chemical rather than purely chemical is suggested by the rapid disappearance of pain on rest. Further confirmation that pain arises from products of muscle metabolism is afforded by the finding that at the height of claudication induced by exercise in a healthy limb which is occluded by a tourniquet, the vessels of the claudicating muscles are fully dilated; and it is known that muscle vessels dilate in response to the accumulation of metabolites and not through a decrease in sympathetic vasoconstrictor tone, which is the mechanism in subcutaneous vessels.

REST PAIN

Rest pain indicates a severe degree of ischæmia in the distal parts of the limb; it is more severe in thromboangiitis than in arteriosclerosis, and it occurs not only after arterial thrombosis in these conditions, but also after arterial embolism.

Rest pain is constant, and is not relieved by recumbency. Indeed it is most severe at night, keeping the patient awake. It is usually situated in the toes and metatarsal region, but in severe cases may involve the foot and lower leg. In character, it is a gnawing, aching pain, to which a hot, burning sensation may be added; it causes extreme distress, and even partial relief is hard to obtain, but not infrequently the patient finds that rest pain is more easily tolerated when the feet are dependent, and he may spend hours at night with the feet dangling over the bedside, or he may attempt to sleep in a chair. As a rule elevation of the limbs above the horizontal increases the pain, but in rare instances the patient may be able to sleep with the feet raised on pillows. In severe cases there is objective sensory loss, but relief is obtained by grasping the toes and foot, or rubbing them with the hands; hours may be spent thus each night. In time, an effect on general body economy becomes apparent and morale is undermined; the patient will not eat, sleep becomes impossible, and he may demand amputation to rid him of his misery. Rest pain may be an indication that gangrene is imminent; there are few patients who, having been forced to attempt sleep in a chair, have preserved their limbs for any length of time. However, not all limbs progress to gangrene, and with rest and care, particularly avoidance of even minimal injury, a number may be nursed back to some degree of usefulness, which

that, after walking a certain distance, he experiences a sense of fatigue in one or other calf; if he continues, this develops into true pain, which is cramp-like and tends to be most severe on the inner aspect of the calf; if he persists further, the pain increases until he is forced to stop and rest; after a short period the pain disappears completely. He may then resume his walk until he has covered the same distance, when the process is repeated. This distance is the "claudication distance", and it is almost constant for any one individual, between 20 yards and 800 yards or more. It is increased if he walks slowly or downhill, and reduced if he walks quickly or uphill; it is commonly shorter in cold weather. It is important to recognize that the pain is relieved by a short period of rest and without change of posture, two points which distinguish it from pain of non-vascular origin.

After the calf, the intrinsic muscles of the foot are those most often affected. The pain is brought on by walking, but it is less cramp-like than calf pain and it is often described as the sensation felt when "crossing pebbles barefoot"; this is because the ischæmia affects not one large muscle, but a number of small muscles which suffer short periods of claudication in turn, and so give rise to this "knobbly" pain. It is quickly relieved by rest. In advanced disease any muscle may claudicate, and pain on exercise has been described in the thigh, gluteal and lumbar muscles. Except in advanced thromboangiitis, it is rare in the upper extremity.

In most cases, the site of claudication indicates the approximate level of the arterial obstruction; if the foot alone claudicates, the obstruction is in the lower leg, whereas if the calf is affected, a popliteal or femoral occlusion will be suspected. In most cases, palpation of the pulses will confirm these suspicions, but occasionally claudication occurs in the calf when distal pulses are present. In this event, the arterial occlusions lie in the sural arteries which supply the two heads of gastrocnemius. These are end arteries, and collateral circulation is not available to meet the needs of exercise. Most muscles have alternative blood supplies, and are therefore less liable to suffer ischæmia, even when the main vessel of the limb is occluded; indeed, circulation within muscles is sometimes increased by occlusion of the main vessel to participate in the bypass, although the main collateral circulation develops in subcutaneous and named branches of the main vessel.

It remains to mention one other factor—arterial spasm—in the causation of ischæmic claudication. That spasm occurs in thromboangiitis is well established, and it is probably a factor in producing ischæmia in younger patients with arteriosclerosis. It is doubtful, however, if spasm ever causes intermittent claudication in the absence of organic arterial disease. In a small number of patients, distal pulses present at rest are temporarily abolished by exercise. This effect must be due to spasm; it is almost certain that these patients, who are usually in the early forties, have organic disease which cannot yet be identified, and they should be treated as patients with

THE PAIN OF ULCERATION: GANGRENE

In obliterative arteritis, injury which may at first appear trivial is the cause in more than half the cases of gangrene. In the majority of patients, the first part to be affected is the tip of a toe and the extent of gangrene may vary from this to the whole foot, the cause of massive gangrene being almost invariably sudden massive thrombosis in a diseased artery. Ulceration is more common in thromboangiitis than in arteriosclerosis, and like gangrene is usually precipitated by trauma. Ischæmic tissues are especially vulnerable to all forms of trauma, whether physical, thermal or chemical; not infrequently, unsuitable treatment by the patient is the precipitating factor. The pain of gangrene is similar to rest pain; its intensity is quite variable. It tends to be more severe in moist gangrene; dry gangrene is usually more painful in thromboangiitis than in arteriosclerosis, in which it is sometimes painless.

The cause of pain in gangrene and ulceration is the process of destruction of tissues, sensory nerve endings and nerve fibres by ischæmia and infection.

TREATMENT OF PAIN IN OBLITERATIVE ARTERITIS

When a main vessel is ligated, nature's response is to develop alternative channels for the maintenance of distal nutrition; these may be adequate or inadequate, according to the site of the block, the age of the patient, the time of injury and other factors, such as loss of blood. From this natural response the principles of treatment of obliterative disease may be deduced. Since it is impossible to "replumb" the limbs, the next best treatment is to foster the development of a collateral circulation, and to provide optimum conditions for its maintenance.

The development of an adequate collateral circulation depends upon four main factors: the level of obstruction, the rate of obstruction, the degree to which collateral vessels themselves are diseased, and the presence or absence of spasm. Arterial spasm is a feature of thromboangiitis and of early arteriosclerosis; it may be a small factor in the older arteriosclerotic, and since it is the only one of the four main factors over which control may be exercised, measures to combat it should be instituted in all patients.

Once begun, the struggle between obliterative process, on the one hand, and collateral circulation and tissue requirements on the other, ends only when the patient dies, although occasionally in thromboangiitis a stage is reached when episodes of arterial obstruction cease. In the great majority of patients the struggle goes on, for a new occlusion at a different level, or a sudden complete occlusion from thrombosis, or an extension of disease to collateral vessels, or spasm induced by exposure to cold, may so tip the scales in favour of the obliterative process that the collateral circulation becomes inadequate for tissue requirements and gangrene results. On the other side, an increased demand by the tissues may find the collateral

will be directly proportional to the extent of collateral circulation which can be fostered and maintained.

Before the onset of true rest pain, there is as a rule a period of weeks or months during which the patient has been conscious that some change in sensation was occurring. This is often difficult to describe, and may be only an "awareness" of his toes; a consciousness of them in a patient who has previously taken them for granted. "Numbness" or a "dead feeling" may be felt, perhaps outlasting the usual effects of cold or exercise to which he has been accustomed; vague tinglings are not uncommon. These symptoms are not true pain, but rather sources of discomfort; they are included because they may be the precursors of true rest pain and, if present in a patient whose main complaint is intermittent claudication, are an indication of distal ischæmia.

Rest pain is the result of severe ischæmia of tissues and of sensory nerve endings. When the latter suffer from ischæmia, the more highly specialized are affected first, as can be demonstrated objectively by testing skin sensitivity. Light touch and light pinprick will not be appreciated in a zone of varying extent, but with proximal margin always circular; the anæsthetic area is of boot, shoe or slipper distribution, or it may be smaller, involving only the forefoot or toes. It will invariably be found that crude forms of sensation, such as deep pinprick or heavy pressure, are appreciated within a territory in which light touch and light pinprick are not; this conforms to the varying vulnerability of different types of sensory nerve endings. The character of rest pain can now be understood: the dull, hot pain is that initiated by the most crude types of end organs, the only ones to survive the ischæmia. That tinglings are felt in the prodromal phase is due to the milder degree of the ischæmia, which has not yet inactivated the more sensitive end organs.

ISCHÆMIC NEURITIS

Ischæmic neuritis is an indication of severe ischæmia. It occurs especially when the site of occlusion is in a proximal segment of a main artery (femoral or external iliac). It may occur after embolism as well as in obliterative arteritis, and may persist for months. The pain tends to be of a shooting, stabbing character. It may follow the course of a large nerve, although its peripheral projection rarely corresponds to the cutaneous distribution of any one nerve. If ulceration or gangrene is present, the sudden, darting pain often originates in its neighbourhood. Ischæmic neuritis tends to cause a flitting type of pain, felt sometimes in one part of the limb, sometimes in another. Constant in the later stages, it may be transient initially and then resembles what has been termed "pre-rest pain".

The cause of ischæmic neuritis is ischæmic degeneration of nerve fibres. It is similar to the cause of rest pain, except that the involvement of the neurones is more proximal; again the less specialized fibres remain longest unaffected.

of warmth, which helps to keep such collateral vessels as are available in a state of vasodilatation. Room temperatures should be between 65° and 70° F.; this is desirable whether the patient is confined to bed or ambulant. Reference has already been made to the need for warm clothes when the patient is able to go out of doors. All these measures are directed towards the provision of optimum conditions for the maintenance of the available collateral circulation in as efficient a state as possible, and towards the elimination of any demand by the tissues which the collateral circulation cannot meet. There are available more specific forms of treatment, the object of which is to amplify those already described.

(2) *Specific Measures*

(a) *Reflex vasodilatation*.—Just as cooling of the hands causes a generalized vasoconstriction, so heating of the hands leads to generalized vasodilatation, provided that the peripheral vessels are not so diseased that dilatation is impossible, as may be the case in older patients with arteriosclerosis. Reflex dilatation is of most value therefore in thromboangiitis and in young patients with arteriosclerosis; it is also of benefit in sudden arterial occlusion. Provided the upper extremities are not involved by the disease, the hand may be warmed by hot-water bottles, a heat-cage, electric pads or, as has been found especially useful, by electrically heated gloves. This form of treatment has its greatest value when the obliterative process is causing rest pain and ischæmic neuritis, and should be maintained for at least six of the waking hours; it is helpful also in the less severe forms of ischæmia and, by helping to open up collaterals, it may slightly increase claudication distance. When the patient is ambulant, before going out of doors it is advisable to secure reflex vasodilatation for one hour.

(b) *Intermittent venous occlusion*.—This measure is also of benefit for rest pain and ischæmic neuritis. By means of a special apparatus, pneumatic cuffs around the upper thighs are inflated for two minutes in every four to a pressure of 35 to 40 mm. Hg. During the compression phase, the venous return is reduced and the limb is filled with arterial blood. It is believed that the amplitude of pulsation in the collateral circulation is increased, but this may be only temporary. On the first day, one hour of treatment is completed; on successive days the treatment is increased by one hour, until eight hours are completed. Intermittent occlusion may be used at night when the patient is sleeping, or by day simultaneously with reflex vasodilatation.

(c) *Postural exercises*.—Various types have been used, the most popular being known as the Buerger-Allen exercises. The limbs are elevated to 45° until full blanching has occurred in the feet; the legs are now held dependent until full rubor develops; then non-weight-bearing foot exercises are performed for two minutes. Each cycle lasts for about four minutes, and six cycles comprise one session, of which three should be performed daily. The refilling of the dependent limbs with fresh arterial blood aids nutrition,

circulation wanting. Exercise may increase muscle requirements so that claudication occurs if the collateral circulation is inadequate. After injury or infection of the tissues, the increased demand for blood is more serious, for if unfulfilled, death of tissue is the result.

Treatment has therefore two main objectives: first, to foster the collateral circulation, and secondly, to prevent the tissues from making excessive demands on that circulation. Treatment is conveniently divided into four sections, of which the last, amputation, is the final resort if the battle is lost.

(1) *General Care*

The patient must be told enough about his condition to enable him to cooperate in treatment. He must pay particular attention to his feet, avoiding even slight injury; the cutting of toenails correctly, the treatment of corns and the wearing of well-fitting shoes and seamless, close-woven woollen socks are important matters. He must avoid crowds. He must avoid exposure to cold, for cold causes vasoconstriction by direct action on arteries and by affecting the whole arterial system through sympathetic nerves, and by the liberation of adrenaline. Not only must he keep the affected limbs warm, but he must avoid chilling of any part of the body, and especially of the hands, because if the hands are allowed to become cold, reflex vasoconstriction may occur in the legs. Clothes must be warm, and to avoid chilling of the leg between knee and sock, long undergarments should be worn. The patient should stop smoking, because even in a normal person the blood flow through a limb is diminished by smoking cigarettes; this is particularly important in thromboangiitis. On the other hand, he must be encouraged to seek beneficial conditions. Rest in bed is essential for the patient with severe rest pain or gangrene; elevation of the head of the bed for six inches induces passive venous congestion, which may limit the extent of gangrene and reduce the agony of rest pain. A cradle should be used to prevent pressure by the bedclothes, which should be left open over the lower end of the cradle, to expose the lower part of the limb to room temperature. Blankets are best made of some cellular material and the sheets should be of flannelette. Above all, it is important to insist that the feet are not directly heated by hot-water bottles or a heat-cage. In the absence of other symptoms, patients with intermittent claudication need not be confined to bed, and indeed a little exercise is beneficial provided that the patient rests before his claudication distance is reached. For any degree of ischæmia, an adequate amount of sleep is essential, because not only is the affected part at rest, but the vessels of the limb are maintained during sleep at the widest possible dilatation; a little whisky or other spirit one hour before bedtime ensures that bed is reached with the vessels already dilated. For severe rest pain, sedation is necessary and codeine has been found useful, although as a last resort it may be necessary to use morphine.

Second in importance to the provision of adequate rest is the provision

of warmth, which helps to keep such collateral vessels as are available in a state of vasodilatation. Room temperatures should be between 65° and 70° F.; this is desirable whether the patient is confined to bed or ambulant. Reference has already been made to the need for warm clothes when the patient is able to go out of doors. All these measures are directed towards the provision of optimum conditions for the maintenance of the available collateral circulation in as efficient a state as possible, and towards the elimination of any demand by the tissues which the collateral circulation cannot meet. There are available more specific forms of treatment, the object of which is to amplify those already described.

(2) *Specific Measures*

(a) *Reflex vasodilatation*.—Just as cooling of the hands causes a generalized vasoconstriction, so heating of the hands leads to generalized vasodilatation, provided that the peripheral vessels are not so diseased that dilatation is impossible, as may be the case in older patients with arteriosclerosis. Reflex dilatation is of most value therefore in thromboangiitis and in young patients with arteriosclerosis; it is also of benefit in sudden arterial occlusion. Provided the upper extremities are not involved by the disease, the hand may be warmed by hot-water bottles, a heat-cage, electric pads or, as has been found especially useful, by electrically heated gloves. This form of treatment has its greatest value when the obliterative process is causing rest pain and ischæmic neuritis, and should be maintained for at least six of the waking hours; it is helpful also in the less severe forms of ischæmia and, by helping to open up collaterals, it may slightly increase claudication distance. When the patient is ambulant, before going out of doors it is advisable to secure reflex vasodilatation for one hour.

(b) *Intermittent venous occlusion*.—This measure is also of benefit for rest pain and ischæmic neuritis. By means of a special apparatus, pneumatic cuffs around the upper thighs are inflated for two minutes in every four to a pressure of 35 to 40 mm. Hg. During the compression phase, the venous return is reduced and the limb is filled with arterial blood. It is believed that the amplitude of pulsation in the collateral circulation is increased, but this may be only temporary. On the first day, one hour of treatment is completed; on successive days the treatment is increased by one hour, until eight hours are completed. Intermittent occlusion may be used at night when the patient is sleeping, or by day simultaneously with reflex vasodilatation.

(c) *Postural exercises*.—Various types have been used, the most popular being known as the Buerger-Allen exercises. The limbs are elevated to 45° until full blanching has occurred in the feet; the legs are now held dependent until full rubor develops; then non-weight-bearing foot exercises are performed for two minutes. Each cycle lasts for about four minutes, and six cycles comprise one session, of which three should be performed daily. The refilling of the dependent limbs with fresh arterial blood aids nutrition,

circulation wanting. Exercise may increase muscle requirements so that claudication occurs if the collateral circulation is inadequate. After injury or infection of the tissues, the increased demand for blood is more serious, for if unfulfilled, death of tissue is the result.

Treatment has therefore two main objectives: first, to foster the collateral circulation, and secondly, to prevent the tissues from making excessive demands on that circulation. Treatment is conveniently divided into four sections, of which the last, amputation, is the final resort if the battle is lost.

(1) *General Care*

The patient must be told enough about his condition to enable him to cooperate in treatment. He must pay particular attention to his feet, avoiding even slight injury; the cutting of toenails correctly, the treatment of corns and the wearing of well-fitting shoes and seamless, close-woven woollen socks are important matters. He must avoid crowds. He must avoid exposure to cold, for cold causes vasoconstriction by direct action on arteries and by affecting the whole arterial system through sympathetic nerves, and by the liberation of adrenaline. Not only must he keep the affected limbs warm, but he must avoid chilling of any part of the body, and especially of the hands, because if the hands are allowed to become cold, reflex vasoconstriction may occur in the legs. Clothes must be warm, and to avoid chilling of the leg between knee and sock, long undergarments should be worn. The patient should stop smoking, because even in a normal person the blood flow through a limb is diminished by smoking cigarettes; this is particularly important in thromboangiitis. On the other hand, he must be encouraged to seek beneficial conditions. Rest in bed is essential for the patient with severe rest pain or gangrene; elevation of the head of the bed for six inches induces passive venous congestion, which may limit the extent of gangrene and reduce the agony of rest pain. A cradle should be used to prevent pressure by the bedclothes, which should be left open over the lower end of the cradle, to expose the lower part of the limb to room temperature. Blankets are best made of some cellular material and the sheets should be of flannelette. Above all, it is important to insist that the feet are not directly heated by hot-water bottles or a heat-cage. In the absence of other symptoms, patients with intermittent claudication need not be confined to bed, and indeed a little exercise is beneficial provided that the patient rests before his claudication distance is reached. For any degree of ischæmia, an adequate amount of sleep is essential, because not only is the affected part at rest, but the vessels of the limb are maintained during sleep at the widest possible dilatation; a little whisky or other spirit one hour before bedtime ensures that bed is reached with the vessels already dilated. For severe rest pain, sedation is necessary and codeine has been found useful, although as a last resort it may be necessary to use morphine.

Second in importance to the provision of adequate rest is the provision

PAIN IN SUDDEN ARTERIAL OCCLUSION

Apart from trauma, sudden arterial occlusion is due either to embolism or to thrombosis. The usual origin of an embolus is cardiac, in auricular fibrillation or myocardial infarction; occasionally a thrombus formed within an artery in obliterative arteritis or in the sac of an aneurysm becomes detached, and passes distally to become impacted as an embolus. In rare instances, a detached venous thrombus passes through a patent foramen ovale and forms a peripheral arterial embolus.

In obliterative arteritis, thrombosis is the mechanism by which vessels become completely occluded; massive sudden thrombosis is thought to occur in about 10 per cent. of patients with thromboangiitis and arteriosclerosis. In the absence of arterial disease, thrombosis sometimes occurs in cardiac disease, in polycythæmia, during infectious diseases and after operations; slowing of the blood and increased tendency to blood-clotting are etiological factors. The differentiation between thrombosis and embolism is impossible, if only the local effects are observed; but if cardiac disease is present, embolism is the most probable diagnosis, whilst obliterative arteritis will favour a diagnosis of thrombosis.

Pain is a feature of sudden arterial occlusion in only about 50 per cent. of patients, and early pain in a smaller number. By early pain is meant sudden severe pain occurring within an hour of the presumed time of occlusion; it is ill-localized and most commonly felt somewhat distal to the level of arterial blockage. It is of little value in the diagnosis of the site of occlusion, which is best made by examination of the pulses. Because early pain may be accompanied by, or overshadowed by, numbness and paræsthesiæ, its description is difficult for the patient. The cause of this sudden pain is not understood, but it is thought to be due to spasm of the main vessel and of collaterals. This hypothesis, for which there is a considerable amount of experimental proof, explains why the ischæmia produced appears to be out of proportion to that expected from obstruction of a major vessel if the collateral circulation were intact; it also explains why early treatment by reflex vasodilatation may improve the condition within a few hours. It is presumed that when sudden arterial occlusion occurs painlessly, spasm does not occur; there is no doubt that ischæmia is more profound when pain occurs. There is no satisfactory explanation why a patient may have a painful embolic episode after a succession of painless ones, although the sensory pathway proximal to the lesion almost certainly must remain intact. It is possible that there are two sensory pathways from the nerve plexus on the vessel wall at the site of occlusion, one in sensory somatic nerves, the other in the nerve plexus surrounding the vessel wall. Reference has already been made to rest pain, ischæmic neuritis and gangrene following sudden arterial occlusion.

Treatment must be immediate; aortic emboli require removal, but thrombosis and embolism elsewhere are best treated conservatively in the first

and the gentle exercises act as a mild stimulus towards the development of a collateral supply, as well as in maintaining muscle tone. Postural exercises are useful for rest pain and for early ulceration or gangrene; if pain is increased, it may be inadvisable to persist with them.

(d) *Sympathectomy*.—This operation should be reserved for patients with thromboangiitis and for younger patients with arteriosclerosis; in the latter condition it should hardly ever be performed over the age of sixty. The object of sympathectomy is to remove the vasoconstrictor influence of the sympathetic nervous system. It is of value in minor ulceration, in rest pain and in ischæmic neuritis, but if the degree of ischæmia is profound, it is advisable to attempt improvement by the measures already described before performing sympathectomy, for if no improvement occurs with simpler measures, sympathectomy will not help. Its effect on claudication is unpredictable, but it may well be of benefit if the main arterial block is in the femoral or external iliac artery, by dilating collateral vessels so that blood is led past the obstruction and returned to the main arterial trunks below the lesion, which is the primary object of any collateral circulation. Before sympathectomy is performed, it is essential to ascertain that vasodilatation will follow it; that is done most simply by inducing reflex vasodilatation and recording the skin temperature of the toes by thermocouples. In favourable cases there may result: (a) an immediate improvement in skin nutrition; (b) lowered vulnerability of distal tissues to trauma so that later gangrene is less probable; (c) the possibility of performing a below-knee amputation if gangrene does occur later; and (d) occasional improvement in claudication.

(e) *Palliative neurectomy*.—A muscle which is paralysed cannot claudicate. The gastrocnemius and part of the soleus may be denervated through an incision in the popliteal fossa (Jepson, R. W., 1948; quoted in *Lancet*, i, 526); the patient need stay in bed for only one or two days. In about 30 personal cases, claudication distance has been substantially increased. Disability is minimal, for the patients already have been restricted by their vascular disease. The operation is suitable for patients who have only slight evidence of distal ischæmia, and is the one of choice for early arteriosclerotics who cannot be improved by sympathectomy.

(f) *Amputation*.—In spite of the measures described above, the obliterative process may overcome the collateral circulation, or distal tissues may find to undue demands on this circulation, so that gangrene occurs. Dead tissue does not become revascularized, so that some loss is inevitable. When ischæmia, an added to a toe, natural separation may be awaited or the toe affected part at rest. When gangrene involves the foot also, amputation is at the widest possible election being the lower third of the thigh. A below-knee amputation ensures a good blood supply is sufficient to secure healing of the wound. For severe rest pain, sedative blood supply is sufficient to secure healing of the wound, although as a last resort it may be necessary to amputate.

Second in importance to the

CLINICAL INFLUENZA

By J. HARTSILVER, M.D., M.R.C.P.

BETWEEN November and April or May, a series of illnesses have occurred in my practice for many years which are classified clinically as influenza. Whether organisms isolated prove to be of the A or B type, or whether atypical viruses can be isolated, is a problem which, owing to circumstances, it has been impossible to solve, but the fact remains that these cases are epidemic at this time of the year, and can be grouped into the following varieties:—

(1) *Febrile influenza*.—Fever with headache, backache and malaise, but especially ushered in by rigors and sweating.

(2) *Respiratory*, whether of the upper or lower respiratory tracts.

(3) *Tonsillitis*, in which tracheitis with swollen and inflamed tonsils predominate, and a typical glazed, granular, reddened area appears on the pharyngeal wall.

(4) "*Gastric*" influenza with nausea and vomiting, occurring with or without enteritis, in which diarrhoea predominates.

These all overlap, two or more groups occurring in one patient. Group (4) is so mixed up with (1), (2) and (3) in families and workers that they are definitely considered as belonging to the epidemic.

SYMPTOMATOLOGY

In all these cases a shivering attack with sweating and headache or backache, with pains in the limbs or behind the eyes, occurs. All the patients were asked if they had these and, with the presence of rigors, this is considered clinically diagnostic. Those who have had previous attacks will walk into the surgery and say they have had the "flu"; they may have treated themselves, and feeling run down afterwards have come for a tonic. It is considered that their diagnosis was a correct interpretation as to the above symptoms being positive.

In all these epidemics that occur from November to May, it may be that some very small minority of the cases would not, on bacteriological investigation, be found to be influenza, but are due to a cold virus, or one of the other organisms found in enteritis or food poisoning. The large majority, however, do correspond closely with what has been considered influenza for many years, and the response to treatment is clearly suggestive that these cases are one and the same disease. Post-influenzal debility, depression, and an odd occasional psychotic change occur. No other sequence or complication ensues, save dyspnoea, due to toxic myocardial change, which improves eventually, and pyrexia, which may be prolonged. This last has persisted on occasions for as long as three to five weeks, but has vanished

instance. The objectives are: first, to prevent further obstruction of the main vessel and its collaterals by extension of thrombosis or formation of thrombus above an impacted embolus; and secondly, to encourage the collateral circulation by the measures already discussed. Immediate anticoagulant therapy is begun by the administration of heparin intravenously; morphine is advisable to avoid vasoconstriction by emotional stimuli; the head of the bed should be raised and reflex vasodilatation instituted. The response to treatment must be most carefully observed, for occasionally a limb which fails to respond to conservative therapy may be saved by embolectomy; the time margin is a matter of hours only and the decision is never easy, but a useful clinical guide is that if improvement does not occur within eight hours, embolectomy should be performed; otherwise gangrene is inevitable.

Brief reference must be made to pseudo-embolism, which occurs characteristically in patients with decompensated cardiac disease. Clinically it is indistinguishable from embolism and thrombosis, and pain is often a marked feature; treatment is instituted as for any sudden arterial occlusion, and in such cases the response is rapid, the distal pulses sometimes returning within a few hours. In the absence of a better explanation, the condition has been attributed to arterial spasm of unknown etiology.

PAIN IN ANEURYSMS OF PERIPHERAL ARTERIES

Excluding trauma, the most common cause of peripheral aneurysm is arteriosclerosis: the usual sites in the lower extremity are in the femoral and popliteal arteries, where distortion of the sclerosed artery by flexion of the hip and knee further weakens the wall. In the upper limb non-traumatic aneurysms are very rare, although in patients with cervical rib an aneurysmal dilatation is not infrequent in the third part of the subclavian artery. Pain caused by peripheral aneurysms results from rupture of the aneurysm, from pressure on nerves or veins, or by the migration of an embolus from the sac.

The aneurysm may be excised; but if this is contemplated, it is imperative to note the condition of the distal pulses. If they are vigorous, the main blood flow is through the aneurysm, in which thrombosis, nature's method of obliterating aneurysms, is at most only minimal; in such a case the collateral circulation is not yet ready to assume responsibility for distal nutrition, and the effect of excision of the aneurysm would be that of sudden arterial occlusion with inadequate collateral channels, so that gangrene would probably ensue. Compression of the vessel proximal to the aneurysm will confirm that the foot quickly becomes ischæmic; before excision every effort should be made to improve the collateral circulation by increasing daily periods of compression of the vessel proximal to the aneurysm, and in selected cases by sympathectomy.

The figures quoted above for influenza are quite apart from the large numbers of patients who are suffering from systematic and localized disease and from the host of conditions met with in general practice.

TREATMENT

Prophylactic.—Contrary to the belief of many writers on influenza, I still consider that quinine and aspirin are specific remedies for prevention as well as for treatment. For many years now, a number of patients who are very susceptible to recurrences which can be most troublesome, have been given 240 minims (14 ml.) doses of ammoniated tincture of quinine (in tablet form), nightly, during the epidemic. When they feel the slightest symptoms coming on, such as shivers, sweats, headache and malaise, 240 minims (14 ml.) of ammoniated tincture of quinine, in tablet or capsule form (if not available, 1 to 2 grains [0.065 to 0.13 g.] of quinine sulphate) with 10 grains (0.65 g.) of aspirin are taken at night. Avoidance of chill, and a little extra rest are all that are required to ward off the attack. Once this has developed, however, aspirin, 10 grains (0.65 g.), and ammoniated tincture of quinine, 120 minims (7 ml.) t.d.s., are given in the febrile cases. Expectorants are prescribed for the chest cases, with a linctus and steam inhalations when necessary. For tonsillitis, aspirin is given to suck, up to 20 or 30 grains (1.3 or 2 g.) a day, and steaming also, to reduce swelling. In influenzal tonsillitis, improvement seldom occurs with sulphonamide drugs or penicillin, whereas aspirin is not only easy to take, but quickly improves the condition. Subsequent chilling grossly aggravates symptoms despite any treatment.

Gastro-intestinal cases.—An alkali sedative, such as morphine with kaolin, bismuth, or a chalk and opium mixture, usually improves the condition rapidly. For nausea and sickness, 1/100 grain (0.65 mg.) of atropine sulphate, three times a day, before food, has been added and seldom fails. Unless improvement occurs in *one day* the diagnosis needs revising.

Convalescence.—Iron, strychnine and arsenic in pill form, with vitamins A, D, and C, are given. Vitamin C is omitted if fruit is obtainable in quantity. For depression, extra rest is important.

SUMMER INFLUENZA

In addition to the winter season there are in June, July and August a number of cases of pyrexia with rigors and pain in the limbs, headache and malaise. Other than a few râles in the chest there are very few physical signs to be observed; sometimes a sore throat and more often some bronchitis is found. Many patients have called this "summer influenza" and they may well be right. Unfortunately there is little or no improvement, and the temperature persists, with treatment by aspirin and quinine, sulphonamide drugs or even penicillin. With several days' rest in bed the condition usually returns to normal. In a few patients, however, pyrexia as

without any definite suggestion as to its cause other than disturbed temperature regulation and a patchy bronchial pneumonia. When latent tuberculosis has become manifest influenza may or may not have caused this to occur.

Cases occurring during the last two years have all proved to be mild. No deaths have occurred, even amongst the aged and very young, and there are many patients aged eighty to ninety, and many infants and children in my practice. No cases of post-influenzal neuritis have occurred as in previous years. Of the abdominal types, only one or two cases each year have proved to be due to other causes: appendicitis rarely, colonic disease, neoplasm, diverticulitis or prostatic disease. Bronchitis and broncho-pneumonia have occurred, also a number of cases of sinusitis, a common and usual complication of upper respiratory tract disease. Rapid recovery was the rule in all except the extraneous conditions mentioned. These provide localizing signs which should not deceive competent observers.

It may be argued that a simple cold in the head might be mistaken for influenza, but it is seldom that a person with an ordinary cold in the head feels too ill to work, and shivers and pain in the back, head or limbs do not usually occur. With sinusitis which often follows a cold in the head, the signs and symptoms are more sharply localized; if treated early a good response follows without the debility which follows influenza.

The figures for 1946-47 and 1948-49 are as follows:—

CLINICAL INFLUENZA

Winter and Spring 1946-47				Winter and Spring 1948-49			
Type				Type			
(1) Febrile	33	(1) Febrile	40
(2) Respiratory	25	(2) Respiratory	10
(3) Gastro-intestinal	13	(3) Gastro-intestinal	10
(4) Tonsillitis	5	(4) Tonsillitis	2
			—				—
Total	76	Total	62
			—				—

A large number of sore throats and colds which occurred at this time would have been classed clinically as influenza, as also patients with sickness and diarrhoea, but all are excluded because of absence of rigors, pains in the head, back or limbs. A number of conditions ending fatally which may have been ushered in by mild influenza are really due to secondary invaders, e.g. otitis media and broncho-pneumonia. This is an opinion expressed on more than one occasion by competent observers: "few deaths certified as due to influenza or influenzal pneumonia really occur outside the severe epidemics as in 1918". They are probably due to broncho-pneumonia.

Variability in temperature and humidity of climate greatly aggravate or ameliorate the severity of the disease.

The figures quoted above for influenza are quite apart from the large numbers of patients who are suffering from systematic and localized disease and from the host of conditions met with in general practice.

TREATMENT

Prophylactic.—Contrary to the belief of many writers on influenza, I still consider that quinine and aspirin are specific remedies for prevention as well as for treatment. For many years now, a number of patients who are very susceptible to recurrences which can be most troublesome, have been given 240 minim (14 ml.) doses of ammoniated tincture of quinine (in tablet form), nightly, during the epidemic. When they feel the slightest symptoms coming on, such as shivers, sweats, headache and malaise, 240 minims (14 ml.) of ammoniated tincture of quinine, in tablet or capsule form (if not available, 1 to 2 grains [0.065 to 0.13 g.] of quinine sulphate) with 10 grains (0.65 g.) of aspirin are taken at night. Avoidance of chill, and a little extra rest are all that are required to ward off the attack. Once this has developed, however, aspirin, 10 grains (0.65 g.), and ammoniated tincture of quinine, 120 minims (7 ml.) t.d.s., are given in the febrile cases. Expectorants are prescribed for the chest cases, with a linctus and steam inhalations when necessary. For tonsillitis, aspirin is given to suck, up to 20 or 30 grains (1.3 or 2 g.) a day, and steaming also, to reduce swelling. In influenzal tonsillitis, improvement seldom occurs with sulphonamide drugs or penicillin, whereas aspirin is not only easy to take, but quickly improves the condition. Subsequent chilling grossly aggravates symptoms despite any treatment.

Gastro-intestinal cases.—An alkali sedative, such as morphine with kaolin, bismuth, or a chalk and opium mixture, usually improves the condition rapidly. For nausea and sickness, 1/100 grain (0.65 mg.) of atropine sulphate, three times a day, before food, has been added and seldom fails. Unless improvement occurs in *one day* the diagnosis needs revising.

Convalescence.—Iron, strychnine and arsenic in pill form, with vitamins A, D, and C, are given. Vitamin C is omitted if fruit is obtainable in quantity. For depression, extra rest is important.

SUMMER INFLUENZA

In addition to the winter season there are in June, July and August a number of cases of pyrexia with rigors and pain in the limbs, headache and malaise. Other than a few râles in the chest there are very few physical signs to be observed; sometimes a sore throat and more often some bronchitis is found. Many patients have called this "summer influenza" and they may well be right. Unfortunately there is little or no improvement, and the temperature persists, with treatment by aspirin and quinine, sulphonamide drugs or even penicillin. With several days' rest in bed the condition usually returns to normal. In a few patients, however, pyrexia as

in influenza will persist longer. One of these cases investigated at hospital was diagnosed "virus pneumonia". The virus may well be a variant, possibly of influenza. The temperature-regulating mechanism of the body similarly seems to be put out of gear by the infection.

Etiological factors which may be considered are: (1) prolonged drought and spread by dust; (2) sudden nocturnal cold spells and chilling; (3) prolonged shortage of meat and fat in those accustomed to plentiful supplies; (4) inability to afford green stuff and fruit which has been scarce and dear most of the summer; (5) overcrowded accommodation and living conditions. The most likely causes of spread, as in most infections, are aggravated by the really dirty handling of food and feeding utensils in this country. Examples of this are: (1) milk and bread left on door-steps and dog-visited areas; (2) dirty wiping of cooking and eating utensils; (3) dirty hands from lack of personal hygiene.

If one may digress, in connexion with the recent drought, it is of interest to note: (1) the sharp drop in attendance of rheumatic and fibrositic patients due to disappearance or alleviation of pain; (2) the increased incidence of fibrositis with cold dry winds; a feature observed for many years.

SUMMARY

A large group of cases, classified from their signs and symptoms, occur with regular epidemic seasonal periodicity. Clinically these are called, "influenza". The symptoms and course of the disease with treatment are recorded. Nothing whatsoever in the way of complications or sequence has occurred to suggest an alternative diagnosis, and uninterrupted recovery has been the rule with the above-mentioned exceptions. Mild epidemics are recorded in which no deaths occurred, and without serious central or peripheral nervous disease. Many practitioners interrogated have similar experiences over a period of years and much the same treatment has been given.

ASSEMBLY OF THE WORLD MEDICAL ASSOCIATION

THE third annual meeting of the World Medical Association was held at B.M.A. House, London, from October 11 to 15, under the presidency of Dr. Charles Hill. Delegates from the national medical associations in 28 countries attended, and observers were present from the World Health Organization, UNESCO, and a number of international medical bodies. The principal discussions were around the further elaboration of an international code of medical ethics (begun in Geneva last year), a voluminous factual report on the facilities for postgraduate medical education in various countries, and an even more voluminous report on social security measures adopted or projected in nearly all the countries represented in the Association. The last report was discussed for a whole day, Dr. H. Guy Dain giving an account of the first experiences of the British National Health Service, followed by delegates from Sweden, the United States, and the Dominions, who described the position in their countries. It was agreed to continue the collection and circulation of this information. Each national medical association is to be asked to furnish details of the total annual cost of national health schemes in operation or proposed in its country, the results of such schemes, and other information, to be published in a quarterly bulletin. The meeting was marked by the utmost amity and goodwill. Dr. Elmer Lee Henderson, of Kentucky, was elected the next President, for the meeting which is to take place in the United States in 1950.

CURRENT THERAPEUTICS

XXIII.—PARA-AMINOSALICYLIC ACID

By M. M. NAGLEY, M.D.

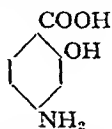
Assistant Senior Physician and Deputy Physician-Superintendent, Grove Park Hospital, London; Tuberculosis Physician, South-Eastern Metropolitan Regional Hospital Board.

Para-aminosalicylic acid (P.A.S.) is a chemotherapeutic substance of comparatively simple chemical structure, but with far-reaching and important effects in certain cases of tuberculosis.

It is proposed therefore to discuss this substance under separate headings, and a summary of its present status is made as a conclusion.

HISTORY

Para-aminosalicylic acid was one of the substances investigated mainly by Lehmann (1946) in his examination of benzoic acid derivatives, following the demonstration by Bernheim (1940, 1941) that sodium salicylate increases the oxygen uptake of tubercle bacilli and that it, or its derivatives, might well be bacillary metabolites of *M. tuberculosis*. In a paper read at the Pasteur Institute in 1947, Lehmann showed that, of more than 50 such derivatives of benzoic acid, it was the *para*-aminosalicylic acid which was, without doubt, the most tuberculostatic—in a molarity of substance in the culture medium of $1:10^{-5}$. The same worker demonstrated that this acid was non-toxic to rats in a concentration of 5 per cent. in their food; that it was highly toxic to guinea-pigs and that it was essential for tuberculostatic action that the amino grouping be at position 4 in the benzene ring. First synthesized by Seidel and Bittner (1902), P.A.S. is to-day manufactured from meta-aminophenol and its formula is:—



The *in vitro* and animal experimental work from Sweden was later abundantly confirmed by Feldman *et al.* (1947), Youmans (1946), Sievers (1946), Alin and Difs (1947), Duca *et al.* (1948), and many other workers. More recently some work has appeared from this country (Gardiner, Rees and Robson, 1949) on the general use of the rabbit's eye for the testing of anti-tuberculous substances, and the results obtained with P.A.S. are given. Apart from this paper, most of the chemical and pharmaceutical studies have come from the Research Department of Herts Pharmaceuticals Ltd. (Simmonite *et al.*, 1948; Goodacre *et al.*, 1948; McAnally and Seymour, 1948) where it has been established that the free acid unbuffered is 80 per cent. decomposed in ten minutes, whereas sodium *para*-aminosalicylate is a much more stable substance. It cannot, however, be sterilized by autoclaving, as decarboxylation occurs with the formation of meta-aminophenol and carbon dioxide. McAnally and Seymour (1948) stressed that the colour of samples of *para*-

aminosalicylic acid bears no relationship to the concentration of sodium *para*-aminosalicylate present, a point which, in the early days of its use, caused much discussion, and was confirmed by Davis (1948). More recently full and most useful statements on the chemistry of P.A.S. have come from Spring (1949) and Drain *et al.* (1949), together with papers presented at the recent British Pharmaceutical Congress, Blackpool, 1949 (Drain *et al.*, 1949; Goodacre and Seymour, 1949; Bavin, 1949).

The large amount of experimental work on this comparatively new tuberculostatic substance has naturally led to its world-wide clinical use. Vallentin (1946), from Gothenberg, summarized his results as "fairly promising", and his work was quickly followed by that of Dempsey and Logg (1947), Ragaz (1948), Erdei and Snell (1948), Steinlin and Wilhelmi (1948), Carstensen and Sjölin (1948), Nagley and Logg (1949) and, more recently, by Vallentin *et al.* (1949), Joules and Nassau (1949), Carstensen and Soderhjelm (1948), together with a series of papers on the combined use of P.A.S. and streptomycin in tuberculosis (which will be discussed later); a recent paper by Hug, Moeschlin and Tanner (1949), which discusses the treatment of bronchial and renal tuberculosis; Smars and Kempe (1949), who discuss tuberculous otitis and its treatment with P.A.S.; Lightbound (1949), who reports a case of lupus vulgaris which responded to P.A.S.; Sivrière (1948), who describes cases of tuberculous pleural effusions managed by P.A.S.; and finally, Witmer and Ragaz (1949), who describe subconjunctival injection of an isotonic solution of P.A.S., which penetrates into the interior chamber of the eye, in the treatment of tuberculous eye conditions, and tuberculous uveitis in particular.

CLINICAL USE

Para-aminosalicylic acid in non-tuberculous conditions

McAnally (personal communication, 1949) reports the disappointing results obtained by the use of P.A.S. in *leprosy* of the lepromatous type generally, and in one case of the tuberculoid type. Although alterations in the morphology of the leprosy bacilli were encountered and a possible reduction in the organism count after P.A.S. treatment, this therapy was not comparable to treatment with sulphetrone. Work is now proceeding on the treatment of leprosy with combined P.A.S. and sulphetrone.

Para-aminosalicylic acid in respiratory tuberculosis

At a recent meeting at Helsinki (Scandinavian Tuberculosis Conference, August, 1949) papers were read on the clinical use of P.A.S., and mention was made by Tørning (personal communication) of full-scale clinical trials of the drug (on the lines of the M.R.C. trials of streptomycin in this country) carried out chiefly in Copenhagen. This work will shortly be published.

A summary will be given here of the consensus of opinion as to the clinical use of this remedy in present-day practice. The sodium salt is used in solution (as opposed to solutions of the free acid) at all times.

Dosage.—For the treatment of pulmonary tuberculosis a dose of 15 to 20 g. per day is given orally, in this country in the form of a solution of the sodium salt in water (often flavoured), in Sweden as granules, and in Switzerland as dragées. The scheme used at Grove Park Hospital is 3 g. every two-and-a-half hours, starting at 9 a.m., and ending at 9.30 p.m., which gives a total of 18 g. per day. This is dispensed as a 20 per cent. solution (1 g. in 5 ml.). At Gothenberg, granules are used in 2 g. doses (for which special scoops are made), each dose being taken at the main meals and with the mid-morning and late evening drinks.

Route.—The drug is usually given orally as described above but can be administered intrapleurally and intravenously, from 10 ml. sterile ampoules of a 20 per cent. solution. The use of P.A.S. in the treatment of tuberculous empyema has not produced the results which might have been expected from the original note by Dempsey and Logg (1947), since it has now been established that the tuberculostatic activity of *para*-aminosalicylic acid is inhibited to an important degree by *para*-aminobenzoic acid, and that therefore it is essential to evacuate all pus from the chest before injecting P.A.S.; no secondarily infecting organism should be present, and a local anaesthetic containing the *para*-aminobenzoic acid radicle must not be used. Conversion of a T.B.-positive fluid to a negative one is, in my experience, not common in the chemotherapy of an empyema, except in the acute, febrile cases of massive, highly bacilliferous effusions occurring during pneumothorax therapy. It is early in the treatment of such cases that P.A.S., together with the other recognized forms of treatment, gives its best results from intrapleural instillation (Davies, 1948).

Types of disease.—The treatment of *acute exudative pulmonary tuberculosis* is the main indication for the use of P.A.S. (Nagley and Logg, 1949) in the dosage already described and, preferably, with concomitant alkalinization of the urine. I have also seen satisfactory results in *tuberculous laryngitis* and *tuberculous endobronchitis* caused by either streptomycin-resistant or non-resistant strains of bacilli, as well as in *tuberculous sinuses*, particularly from post-thoracoplasty wound infections, when a sterile jelly of the following formula has been used (Oberweger, 1949):—

Sodium <i>para</i> -aminosalicylic acid	20	g.
Tragacanth	0.4 g.
Sodium metabisulphite	0.1 g.
Glycerin	0.5 g.
Water	to 100 g.

And more recently, a jelly with methylcellulose substituted for the tragacanth.

There are also reports of P.A.S. having been used intrathecally and intravenously in *miliary tuberculosis* (Carstensen and Soderhjelm, 1948) and interperitoneally (55th Congress of Internal Medicine, Wiesbaden, 1949, and N.A.P.T. Congress, London, 1949). Success cannot be expected with the use of P.A.S. in any type of fibrous or caseous disease, owing mainly to the difficulty of achieving an adequate concentration of the drug at the necessary point, and to the fact, as demonstrated by Alin and Helander

aminosalicylic acid bears no relationship to the concentration of sodium *para*-aminosalicylate present, a point which, in the early days of its use, caused much discussion, and was confirmed by Davis (1948). More recently full and most useful statements on the chemistry of P.A.S. have come from Spring (1949) and Drain *et al.* (1949), together with papers presented at the recent British Pharmaceutical Congress, Blackpool, 1949 (Drain *et al.*, 1949; Goodacre and Seymour, 1949; Bavin, 1949).

The large amount of experimental work on this comparatively new tuberculostatic substance has naturally led to its world-wide clinical use. Vallentin (1946), from Gothenberg, summarized his results as "fairly promising", and his work was quickly followed by that of Dempsey and Logg (1947), Ragaz (1948), Erdei and Snell (1948), Steinlin and Wilhelmi (1948), Carstensen and Sjolín (1948), Nagley and Logg (1949) and, more recently, by Vallentin *et al.* (1949), Joules and Nassau (1949), Carstensen and Soderhjelm (1948), together with a series of papers on the combined use of P.A.S. and streptomycin in tuberculosis (which will be discussed later); a recent paper by Hug, Moeschlin and Tanner (1949), which discusses the treatment of bronchial and renal tuberculosis; Smars and Kempe (1949), who discuss tuberculous otitis and its treatment with P.A.S.; Lightbound (1949), who reports a case of lupus vulgaris which responded to P.A.S.; Sivrière (1948), who describes cases of tuberculous pleural effusions managed by P.A.S.; and finally, Witmer and Ragaz (1949), who describe subconjunctival injection of an isotonic solution of P.A.S., which penetrates into the interior chamber of the eye, in the treatment of tuberculous eye conditions, and tuberculous uveitis in particular.

CLINICAL USE

Para-aminosalicylic acid in non-tuberculous conditions

McAnally (personal communication, 1949) reports the disappointing results obtained by the use of P.A.S. in *leprosy* of the lepromatous type generally, and in one case of the tuberculoid type. Although alterations in the morphology of the leprosy bacilli were encountered and a possible reduction in the organism count after P.A.S. treatment, this therapy was not comparable to treatment with sulphatrone. Work is now proceeding on the treatment of leprosy with combined P.A.S. and sulphatrone.

Para-aminosalicylic acid in respiratory tuberculosis

At a recent meeting at Helsinki (Scandinavian Tuberculosis Conference, August, 1949) papers were read on the clinical use of P.A.S., and mention was made by Tørning (personal communication) of full-scale clinical trials of the drug (on the lines of the M.R.C. trials of streptomycin in this country) carried out chiefly in Copenhagen. This work will shortly be published.

A summary will be given here of the consensus of opinion as to the clinical use of this remedy in present-day practice. The sodium salt is used in solution (as opposed to solutions of the free acid) at all times.

discussing the history of this chemotherapeutic agent mention has been made of its use in tuberculosis of the ear and eye as well as of the renal tract, and it must be noted that P.A.S. has also been given in the treatment of tuberculous peritonitis, pericarditis (Vallentin *et al.*, 1949), and by local instillation into infected joint spaces, abscesses and bones, with good local results. I have had gratifying results in the local use of P.A.S. in tuberculous glands of the neck.

DRUG RESISTANCE

No convincing case has been made in the literature for the development of P.A.S.-resistant strains of *Mycobacterium tuberculosis*, and it is generally accepted that the phenomenon of resistance to this drug does not exist. The emergence of resistant strains to streptomycin of *M. tuberculosis*, *H. influenzae*, *E. coli*, and other organisms, is the great limiting factor in treatment with this antibiotic, and there is no doubt that in the case of *M. tuberculosis*, P.A.S. is active against streptomycin-resistant organisms (Youmans, 1946; Vennesland, Ebert and Bloch, 1948), an experimental finding which has been confirmed in clinical practice. This failure of P.A.S. to produce resistant strains is one of its chief advantages in the treatment of pulmonary tuberculosis.

P.A.S. AND STREPTOMYCIN

The relationship between the antibiotic streptomycin and the chemotherapeutic agent *para*-aminosalicylic acid is one of the most important problems in the study of the chemotherapy of tuberculosis. In the present state of knowledge, no patient with any form of miliary tuberculosis, tuberculous laryngitis, or tuberculous tracheo-bronchitis should be denied streptomycin, but in all other types of acute pulmonary tuberculosis the use of P.A.S. should be seriously considered before exposing the patient—and later the general public—to the possibility that streptomycin-resistant strains will predominate in the sputum. The benefits to the patient in the relief of his symptoms and the reduction in the exudative nature of his disease with P.A.S. therapy are now commonplaces of sanatorium practice; the fact that treatment with this compound can enable patients to come to collapse therapy is also well established (Nagley and Logg, 1949).

No chemotherapeutic agent—antibiotic or otherwise—can yet be said to have replaced the accepted forms of treatment in pulmonary tuberculosis—bed rest, sanatorium regime, collapse therapy, major surgery. For patients, in whom it is thought that a resection or a thoracoplasty will be indicated, streptomycin should be withheld if the initial character of the disease and the patient's condition allow it, in favour of a trial with P.A.S., so that the essential use of streptomycin can be deferred either as a cover for resection or in the event of a postoperative spread after thoracoplasty.

Infinitely more important and far-reaching in its ultimate consequences is the work now being done on the combined use of P.A.S. and streptomycin

(1948), that when elastic fibres in the lung tissue are severed and partly destroyed, e.g., in caseous tuberculous areas, the quantities of P.A.S. laid down are small; the distribution of P.A.S. (as examined by fluorescence microscopy of lung) is mainly in the elastic tissue.

Side-effects.—The institution of P.A.S. therapy is often characterized by gastro-intestinal disturbances, usually with diarrhoea, tending to subside within seven days and only very rarely necessitating temporary discontinuation of the treatment. No other serious side-effects have been reported, apart from an increase in the prothrombin time by Swanson (1949), who was using P.A.S. in a clinical trial on cases of rheumatoid arthritis. I have done careful prothrombin estimations in many cases, and although a hypoprothrombinæmia is usually manifest in those receiving P.A.S., no hæmorrhagic tendency has been noted. One particular case has had a prothrombin time exceeding five minutes with no untoward result. The effect is therefore thought to be without clinical significance, but there would seem to be scope for work in this connexion in the use of P.A.S. in patients who are bleeding. Very occasional cases of P.A.S. crystalluria have been seen and, even more rarely, a skin rash. P.A.S. is remarkably free from important side-effects or toxic effects in man and has been given, in many hospitals, without interruption for many months and even years without untoward results.

Clinical response.—The sequence of events in the treatment of a case of acute exudative type pulmonary tuberculosis is as follows:—

Reduction in temperature within a few days

Reduction in sputum within seven to fourteen days

Diminution in bacillary count

Improvement in the patient's general feeling of well-being

Improvement in general condition and weight

Improvement in the radiological picture

It can be seen that radiological clearing lags well behind the constitutional improvement and may not become manifest for several months after the institution of treatment. High-grade fevers tend to resolve quickly and low-grade pyrexias slowly, if at all. Sputum conversion occurs in approximately 20 per cent. of cases, although some reports (Vallentin, *et al.*, 1949) give a somewhat higher figure. Re-expansion of atelectatic segments can often be demonstrated, due to the healing of an associated bronchial tuberculosis, as well as diminution in the size of tension cavities.

In cases of miliary tuberculosis it has been shown that patients with tuberculous meningitis have been kept alive for some months on P.A.S. alone, but it would seem that streptomycin cannot possibly be denied to such patients, although it is becoming a general tendency in Sweden to treat this form of the disease with combined P.A.S. and streptomycin therapy, using the P.A.S. continuously and the streptomycin in short courses (Carstensen and Soderhjelm, 1948; Lehman, 1949).

Para-aminosalicylic acid in non-respiratory tuberculous conditions.—In

"end point" of research into the chemotherapeutic treatment of tuberculosis, particularly in so far as P.A.S. itself and its compounds can now be brought into line with the recent advances by Domagk (1947), Moncorps and Kalkoff (1947), Hoggarth *et al.* (1949), Malluche (1949), and other workers in the use of thiosemicarbazone products of *p*-acetamidobenzaldehyde. The tremendous activity *in vitro* of thiosemicarbazone derivatives of compounds closely related to P.A.S. augurs well for the future chemotherapeutic attack against tuberculosis; indeed one such compound has been carefully investigated and reported upon (Goodacre and Seymour, 1949).

Mention is made of the use of P.A.S. in non-tuberculous conditions, particularly in leprosy, in which disease, although initial results are disappointing, much more work needs to be done.

Treatment of non-respiratory tuberculosis with P.A.S. is generally considered to be of value, particularly in tuberculous states of the abdomen (e.g. peritonitis and enteritis) and of the pericardium.

Bibliography

- Alin, K., and Difs, H. (1947): *Nord. Med.*, 33, 151.
 —, and Helander (1948): *Acta tuberc. scand.*, 22, 285.
 Bavin, E. M. (1949): *Pharm. J.*, 163, 271.
 Bernheim, F. (1940): *Science*, 92, 204.
 — (1941): *J. Bact.*, 41, 387.
 — (1942): *J. biol. Chem.*, 143, 383.
 Bratton, A. C., Marshall, E. J. Jun., (1939): *Ibid.*, 128, 537.
 Bray, H. G., Ryman, B. E., and Thorpe, W. V. (1948): *Nature*, 162, 64.
 Capon, N. B., and Todd, R. M. (1949): *The Practitioner*, 162, 414.
 Carpenter, C. M., *et al.* (1945): *Proc. Soc. exp. Biol. Med.*, 60, 168.
 Carstensen, B., and Soderhjelm, G. (1948): *Nord. Med.*, 40, 2039.
 —, and Sjolén, S. (1948): *Svenska Lakartidn.*, 45, 729.
 Davies, Morriston (1948): *Thorax*, 3, 189.
 Davis, H. (1948): *Mon. Bull. Min. Hlth.*, 7, 109.
 Dempsey, T. G. (1948): *see Tubercle*, 29, 215.
 —, and Logg, M. H. (1947): *Lancet*, ii, 871.
 Domagk, G. (1947): *Z. ges. Gynæk. Geburtsh.*, 69, 833.
 Drain, D. J., Goodacre, C. L., and Seymour, D. E. (1949): *Pharm. J.*, 163, 271.
 —, Martin, D. D., *et al.* (1949): *J. chem. Soc.*, 6, 1498.
 Duca, C. J., William, R. D., and Scudi, J. V. (1948): *Proc. Soc. exp. Biol., N.Y.*, 67, 159.
 Erdei, A., and Snell, W. E. (1948): *Lancet*, i, 791.
 Erlenmeyer, H., Sorkin, T. J., and Suter, E. (1948): *Helv. chim. Acta*, 31, 988.
 Feldman, W. H., Karlson, A. G., and Hinshaw, H. C. (1947): *Proc. Mayo Clin.*, 22, 473.
 Gardiner, Rees, and Robson, J. M. (1949): *Brit. J. Pharmacol.*, 4, 209.
 Goodacre, C. L., and Seymour, D. E. (1949): *Pharm. J.*, 163, 271.
 —, and Mitchell, B. W. (1948): *J. Pharm. Pharmacol.*, 21, 301.
 Graessle, O. E., and Pietrowski, J. J. (1949): *J. Bact.*, 57, 459.
 Hacker, G. (1948): *Tuberkulosearzt*, 2, 609.
 Hoggarth, E., *et al.* (1949): *Brit. J. Pharmacol.*, 4, 248.
 Hug, R., Moeschlin, S., and Tanner, A. (1949): *Schweiz. med. Wschr.*, 79, 353.
 Ivanovics, G., (1949): *Proc. Soc. exp. Biol., N.Y.*, 70, 462.
 Joules, F. E., and Nassau, E. (1949): *Tubercle*, 30, 98.
 Karlson, A. S., *et al.* (1949): *Proc. Mayo Clin.*, 24, 85.

in tuberculous conditions, particularly in view of the fact—now accepted in American experimental stations—that the emergence of streptomycin-resistant strains of *M. tuberculosis* H37Rv is greatly retarded by relatively low concentrations of P.A.S. (Graessle and Pietrowski, 1949). This work on combined therapy stems from two main sources: first, from the principle underlying the findings, particularly by Carpenter *et al.* (1945), that *N. gonorrhææ* exposed to a combination of four antibacterial agents did not develop resistance, whereas resistance did develop on exposure of the organism to each drug alone; and secondly, from the theoretical consideration that the mode of action of P.A.S. and of streptomycin on the tubercle bacillus is essentially of a different nature in each case, thus an additive action is obtained when the drugs are used in combination in tuberculous animals (Youmans *et al.*, 1947; McClosky, Smith and Frias, 1948).

Clinical work on combined therapy is mentioned as being of great importance by several writers (Capon and Todd, 1949; Madigan *et al.*, 1947), but reports are somewhat limited. Steinlin and Wilhelmi (1948) describe their results with P.A.S. and streptomycin combined from Switzerland, Paraf, *et al.* (1948) from Paris, and Karlson *et al.* (1949) from the Mayo Clinic.

SUMMARY

Para-aminosalicylic acid is a valuable addition to our armamentarium of tuberculostatic substances which are of clinical value.

A review of the history of the development of our knowledge in this field has been made and an estimate attempted of its present status in the treatment of tuberculous conditions. P.A.S. would seem primarily to be indicated in acute forms of pulmonary tuberculosis of the exudative type, when an improvement in the patient's general condition, temperature, blood sedimentation rate, and weight can confidently be expected. A tendency to radiological chronicity of the lung lesions and the development of the X-ray appearances results (Nagley and Logg, 1949).

Although not as active as streptomycin, P.A.S. has the dual advantage of being tuberculostatic to streptomycin-resistant strains and of failing *per se* to produce P.A.S.-resistant strains. Thus it is of value in acute tuberculous conditions in which streptomycin has proved of little avail, after resistant strains have emerged or become predominant, or in those cases in which streptomycin therapy should be deferred until a later stage in treatment.

The combined use of P.A.S. and streptomycin in the treatment of all forms of tuberculosis is mentioned, and it should be stressed here that P.A.S. is not merely a substance which delays the emergence of streptomycin-fast organisms (although this is a vital consideration and needs rapid clinical confirmation), but is itself a proved tuberculostatic substance and therefore has its part to play in the chemotherapy of the disease on the basis of its own mode of action.

P.A.S. is a substance which is at the "starting point" rather than at the

REVISION CORNER

MODERN METHODS IN THE TREATMENT OF VARICOSE ULCERS

FEW benign conditions give rise to so much discomfort and economic loss as does varicose ulceration of the legs. It is therefore important to have a clear idea of the mechanism by which these ulcers are produced and to apply a reasoned and systematic method of treatment in their cure.

PATHOLOGY

Homans (1917) described three types of varicose ulceration: (1) ulcers of superficial varices; (2) ulcers of superficial varices accompanied by incompetence of the communicating veins, of non-inflammatory origin; and (3) ulceration following thrombophlebitis of the deep veins of the leg, complicating pregnancy, fevers, operation or fractures. In all these groups the fundamental cause is the same, i.e. inadequate circulation leading to venous stasis, poor oxygenation of the tissues, accumulation of metabolites, œdema and lymph stasis, whilst in later life an additional factor may be a poor arterial supply due to arteriosclerosis of the peripheral arteries. The skin of the lower part of the leg, subjected to these conditions and possessing, at the best, a relatively poor arterial supply, becomes eczematous and finally ulcerates. This ulceration tends to persist and spread owing to the continuance of the causal factors which prevent healing, and the superimposition of infection. When, in addition to stasis of blood in the superficial veins, there are changes in the deep veins as a result of thrombophlebitis, or a diminished arterial supply to the limb due to arteriosclerosis, the conditions favouring the occurrence and spread of ulcerations are greatly increased, and the problem of obtaining healing of the ulcers under these conditions is correspondingly more difficult.

ASSESSMENT OF CASES

In assessing cases of varicose ulceration before treatment certain investigations should be carried out. These include: (a) the well-known Brodie-Trendelenburg test for determining the competence or otherwise of the valves of the saphenous system and their deep communications; (b) Perthes' test, which indicates whether or not the venous return in the deep veins is impaired; and (c) palpation of the pulses at the ankle. The general condition of the patient must also be investigated. Examination of the urine to exclude albuminuria and glycosuria, a Wassermann test, and a hæmoglobin and red-cell estimation should be carried out in all cases. Not infrequently a degree of anæmia is present which requires correction.

CONSERVATIVE TREATMENT

In determining the method of treatment to be adopted the various factors which may initiate and perpetuate the ulcer should be remembered. These are incompetence of the superficial veins, obliteration of the deep veins, œdema and infection, and arterial insufficiency.

Local treatment of the ulcer and the accompanying œdema should be begun forthwith. The modern view is that all such treatment should be ambulatory, and in the vast majority of cases this is possible. Only when there is gross œdema associated with thrombophlebitis should rest in bed with the limb elevated be enjoined. To abolish the œdema and cover the ulcer, some form of elastic adhesive bandage, such as "elastoplast", is employed. The ulcer is covered with a piece of adhesive sponge rubber of such a size as to overlap it generously all round, and the bandage is applied firmly to the leg from the base of the toes to just below the knee.

- Klyne, W., and Newhouse, J. P. (1948): *Lancet*, ii, 611.
 Lehmann, J. (1946a): *Ibid.*, i, 15.
 — (1946b): *Svenska Lakartidn.*, 43, 2029.
 — (1947a): *Rev. gen. Sci.*, 54, 222.
 — (1947b): *Nord. Med.*, 33, 140.
 — (1949): *Proc. N.A.P.T. Congr.* (In the press).
 Lemming, R. (1949): *Lancet*, i, 200.
 Levaditi, C., Girard, A., and Vaisman, A. (1948): *Bull. Acad. Méd. Paris*, 132, 210.
 Lightbound, T. (1949): *Lancet*, i, 937.
 Lutz, G. (1949): *Ann. Inst. Pasteur*, 76, 150.
 McAnally, D., and Seymour, D. E. (1948): *Lancet*, i, 303.
 McClosky, W. T., Smith, M. I., and Frias, J. E. G. (1948a): *Fed. Proc.*, 7, 244.
 — (1948b): *J. Pharmacol.*, 92, 447.
 Madigan, D. G., et al. (1947): *Lancet* ii, 897.
 Malluche, H. (1949): *Med. Klinik.*, 44, 225.
 Moeschlin, S., Jaccard, G., and Bosshard, M. (1948): *Experientia*, 4, 158.
 —, and Schreiner, W. (1949): *Schweiz. med. Wschr.*, 79, 117.
 Moncorps, C., and Kalkoff, K. W. (1947): *Med. Klin.*, 21/22, 812.
 Nagley, M. M., and Logg, M. H. (1949): *Lancet*, i, 913.
 Oberweger, K. H. (1949): *Pharm. J.*, 163, 36.
 O'Connor, J. A. (1948): *Post-grad. med. J.*, 24, 455.
 Paraf, J., Desbordes, J., and Paraf, M. (1948): *Bull. Mém. Soc. Méd. Hôp. Paris*, 64, 830.
 Ragaz, L. (1948): *Schweiz. med. Wschr.*, 78, 332.
 Rosdahl, F. (1948): *Särl. svensk. Tidskr.*, 60, 64.
 Scarzello, M., and Sormano, G. P. (1948): *Pediatrics, Naples*, 10, 12.
 Seidel, and Bittner (1902): *M Schr. Chem.*, 23, 423.
 Seiler, M. (1949): *Tubercle*, 30, 45.
 Sievers, O. (1946): *Svenska Lakartidn.*, 43, 2041.
 — (1949): *Lancet*, i, 798.
 Simmonite, D., Seymour, D. E., and Oberweger, K. H. (1948): *J. Pharm. Pharmacol.*, 21, 292.
 Sivrière, A. (1948): *Presse Méd.*, 56, 791.
 Smars, E., and Kempe, S. G. (1949): *Nord. Med.*, 41, 649.
 Spring, S. S. (1949): *Edinb. med. J.*, 56, 237.
 Steinlin, H., and Wilhelmi, E. (1948): *Schweiz. med. Wschr.*, 78, 1219.
 Suter, E. (1948): *Ibid.*, 78, 324.
 Swanson, J. (1949): *Lancet*, ii, 175.
 Tennent, D. M., and Leland, M. L. (1948): *Fed. Proc.*, 7, 195.
 Tobie, W. C. (1948): *Amer. Rev. Tuberc.*, 58, 693.
 Vallentin, G. (1946): *Svenska Lakartidn.*, 43, 2047.
 — (1947): *Nord. Med.*, 33, 147.
 —, et al. (1949): *Le Poumon.*, 5, 193.
 Venkataraman, A., Venkataraman, P. R., and Lewis, H. B. (1948): *J. biol. Chem.*, 173, 641.
 Vennesland, W., Ebert, R. M., and Bloch, R. G. (1948): *Proc. Soc. exp. Biol., N. Y.*, 68, 250.
 Veran, E., and Hautefeuille, P. E. (1949): *Rev. Tuberc.*, 13, 280.
 Way, E. L., Weiss, R., Howie, D. L., and Smith, K. (1948): *Fed. Proc.*, 7, 263.
 —, —, and Swanson, R. (1948): *J. Pharmacol.*, 93, 368.
 Widstrom, G. V. (1947): *Nord. Med.*, 43, 2153.
 —, and Swedberg, H. (1947): *Ibid.*, 43, 2148.
 Witmer, H., and Ragaz, L. (1949): *Schweiz. med. Wschr.*, 79, 452.
 Youmans, G. P. (1946): *Quart. Bull. Nthwest. Univ. med. Sch.*, 20, 420.
 —, Youmans, A. S., and Osborne, R. R. (1947): *Journal-Lancet*, 67, 403.
 —, Raleigh, G. W., and Youmans, A. S. (1947): *J. Bact.*, 54, 409.
 Zetterburg, P. (1948): *Upsal. Lakarebor Forhandling*, 5, 157.

REVISION CORNER

MODERN METHODS IN THE TREATMENT OF VARICOSE ULCERS

FEW benign conditions give rise to so much discomfort and economic loss as does varicose ulceration of the legs. It is therefore important to have a clear idea of the mechanism by which these ulcers are produced and to apply a reasoned and systematic method of treatment in their cure.

PATHOLOGY

Homans (1917) described three types of varicose ulceration: (1) ulcers of superficial varices; (2) ulcers of superficial varices accompanied by incompetence of the communicating veins, of non-inflammatory origin; and (3) ulceration following thrombophlebitis of the deep veins of the leg, complicating pregnancy, fevers, operation or fractures. In all these groups the fundamental cause is the same, i.e. inadequate circulation leading to venous stasis, poor oxygenation of the tissues, accumulation of metabolites, œdema and lymph stasis, whilst in later life an additional factor may be a poor arterial supply due to arteriosclerosis of the peripheral arteries. The skin of the lower part of the leg, subjected to these conditions and possessing, at the best, a relatively poor arterial supply, becomes eczematous and finally ulcerates. This ulceration tends to persist and spread owing to the continuance of the causal factors which prevent healing, and the superimposition of infection. When, in addition to stasis of blood in the superficial veins, there are changes in the deep veins as a result of thrombophlebitis, or a diminished arterial supply to the limb due to arteriosclerosis, the conditions favouring the occurrence and spread of ulcerations are greatly increased, and the problem of obtaining healing of the ulcers under these conditions is correspondingly more difficult.

ASSESSMENT OF CASES

In assessing cases of varicose ulceration before treatment certain investigations should be carried out. These include: (a) the well-known Brodie-Trendelenburg test for determining the competence or otherwise of the valves of the saphenous system and their deep communications; (b) Perthes' test, which indicates whether or not the venous return in the deep veins is impaired; and (c) palpation of the pulses at the ankle. The general condition of the patient must also be investigated. Examination of the urine to exclude albuminuria and glycosuria, a Wassermann test, and a hæmoglobin and red-cell estimation should be carried out in all cases. Not infrequently a degree of anæmia is present which requires correction.

CONSERVATIVE TREATMENT

In determining the method of treatment to be adopted the various factors which may initiate and perpetuate the ulcer should be remembered. These are incompetence of the superficial veins, obliteration of the deep veins, œdema and infection, and arterial insufficiency.

Local treatment of the ulcer and the accompanying œdema should be begun forthwith. The modern view is that all such treatment should be ambulatory, and in the vast majority of cases this is possible. Only when there is gross œdema associated with thrombophlebitis should rest in bed with the limb elevated be enjoined. To abolish the œdema and cover the ulcer, some form of elastic adhesive bandage, such as "elastoplast", is employed. The ulcer is covered with a piece of adhesive sponge rubber of such a size as to overlap it generously all round, and the bandage is applied firmly to the leg from the base of the toes to just below the knee.

This bandage is left on for one to two weeks, any discharge being removed by sponging, or absorbed by a dressing applied over the bandage. The patient is encouraged to be as active as possible as the circulation is thereby improved and the œdema lessened. The bandage is changed only when it has become loose owing to the subsidence of the œdema or the amount of discharge makes it necessary to renew it.

In some patients the skin is hypersensitive to these bandages and in such cases some form of Unna's paste bandage should be employed. Such bandages are now available commercially ("viscopaste" and "ichthopaste" bandages) and are applied to the limb without tension from the base of the toes to the knee. The bandage is then covered by a firmly applied crêpe bandage, which adds the necessary elastic support.

Infection.—It has been claimed that, with the technique described, the presence of infection is of small consequence, that in fact the discharge from the ulcer is beneficial. It is reasonable to think, however, that when the infection can be eliminated, healing will be more rapid and more certain. This infection is usually due to the *coli-proteus-pyocyanus* group. Until recently, few substances were of much value against these organisms. However, the various sulphonamides in powder form and, more recently, the diamidine compounds and streptomycin have proved of considerable value; now that streptomycin has become more generally available it should be of great assistance in these cases of chronic ulceration in which infection is an important element in preventing healing. These substances are applied topically to the ulcer before the limb is bandaged.

OPERATIVE TREATMENT

The measures outlined above are continued until the ulcer has healed or a stage has been reached at which further measures are required to ensure healing.

Superficial varicosities—Following healing, or when the œdema and infection have subsided, but healing is delayed, and when Perthe's test shows little or no obstruction to the deep veins, the superficial varicosities must be systematically obliterated. If the Brodie-Trendelenburg test indicates incompetence of the valves in the main saphenous trunk, high ligation and division of the saphenous vein together with all its tributaries at the fossa ovalis should be undertaken. If there is incompetence of the communicating veins, further ligation and division lower down is required. Retrograde injection of the saphenous vein with a sclerosing solution such as ethanalamine oleate is carried out at the same time. If local varices only are present, and in those cases in which retrograde injection at the time of ligation has not obliterated all the varicosities, local injection of the sclerosing fluid into these varices should be done.

When the ulcer does not heal with these methods further operative measures are required. These aim at: (a) providing a new epithelial covering for the ulcer; (b) increasing the blood supply to the limb; or (c) improving the lymphatic drainage of the limb. Any one or more of these procedures may be employed in an individual case.

Skin-grafting.—This is the obvious method to use to obtain healing and it is frequently successful. Split skin (Tiersch) grafts cut into postage stamp size, or pinch (Reverdin) grafts are distributed over the surface of the ulcer and are kept in place by a pressure dressing. Skin-grafting may, in selected cases, be preceded by one or other of the measures mentioned below.

Lumbar sympathectomy.—The value of sympathectomy in the treatment of stubborn ulcers has been the subject of debate. Attention has again been drawn to this procedure recently by Borrie and Barling (1948), who claimed good results in a number of cases of long-standing ulceration. Cases suitable for this operation require careful selection; those in which a cold limb with local cyanosis and a moist sweating skin are prominent features are likely to show a good result.

Cases characterized by a stubborn brawny œdema and ulcers with callous and avascular base are unlikely to benefit from sympathectomy. In these Bancroft *et al.* (1940) advise the use of a modified Kondoleon operation, in which longitudinal incisions are made in the leg down to healthy tissue, the resulting defects being subsequently covered by skin grafts. They record healing in a number of cases which resisted other forms of treatment.

Ulcers associated with deep thrombophlebitis.—Those cases in which there is a history of deep thrombophlebitis, and in which Perthe's test indicates obstruction in the deep veins, are the most difficult to treat satisfactorily. Ligature and injection of the superficial veins are contraindicated, and in such cases conservative treatment with elastic bandaging and the use of antibacterial agents should be tried. Should these measures fail, lumbar sympathectomy, followed by skin-grafting, may be effective. It is to be hoped, however, that this type of case will become more and more uncommon as the use of the anticoagulants (heparin and dicoumarol) becomes more widespread in the treatment of the initial lesion.

In all cases in which healing has been obtained, it is advisable that the patient should continue to wear some form of elastic support for the leg, to assist the venous return and minimize the possibility of trauma to the skin.

IAN MACKENZIE, M.B., F.R.C.S.ED.

References

- Bancroft, F. W., Stanley-Brown, M., and Taylor, R. F. (1940): *Ann. Surg.*, **III**, 874.
 Borrie, J., and Barling, E. V. (1948): *Brit. med. J.*, **ii**, 203.
 Homans, J. (1917): *Surg. Gynec. Obstet.*, **24**, 300.

THE TREATMENT OF BURNS

In the anxious search for a standard regime in the care of burns, treatment is constantly changing. This search for a universal method is doomed to failure since no two burns are the same, varying in extent, depth, site, the age of the patient and the local and general reaction to the injury. From work in recent years, however, certain broad principles have emerged and some methods of local treatment have proved their value. It is the purpose of this brief article merely to outline present trends.

FIRST-AID TREATMENT

To reduce the chances of introduction of infection elaborate first-aid treatment should be avoided. The burned area should be wrapped in sterile dry dressings or freshly laundered linen without removal of the clothes. Morphine, if required to relieve pain, should be given intravenously.

SHOCK

On reaching hospital the area of the burn is assessed, using some such chart as Berkow's or a modification of it which allows for the variation in the proportions of the body at different ages. Shock can be expected in burns which involve more than 10 per cent. of the surface in adults or more than 5 per cent. in the case of children under ten years. Such cases are admitted to a special "shock room", where this exists, and certainly under the care of a special nurse, who records frequent serial readings of temperature, pulse, respiration, blood pressure and hæmatocrit examinations. Accurate records of fluid intake and output are also kept.

Intravenous fluid therapy.—Since shock is due to loss of plasma into the burned area and a consequent fall in the circulating blood volume, and since the process is soon irreversible, intravenous fluid therapy is started forthwith. Normal saline or 5 per cent. glucose in normal saline should be given initially, since there is some evidence that sodium ions administered as isotonic sodium chloride are of value in preventing shock in burn cases. The infusion may then be continued with plasma.

In assessing the probable fluid requirements before the actual onset of shock some sort of formula is useful as a rough guide. In adults, one method is to give 100 ml. for each percentage of body burned over 10 per cent., half of this being administered quickly and the remainder by drip. Thereafter the administration of fluids is controlled by the clinical condition and serial hæmatocrit readings, plasma usually being continued while the tendency to hæmoconcentration persists.

The danger of pulmonary complications from overloading with fluid must be constantly borne in mind. The patient should be encouraged to take fluids by mouth. If anoxæmia is present, oxygen should be administered by nasal tube.

LOCAL TREATMENT

After the institution of resuscitation therapy attention is turned to the burn itself. From the therapeutic point of view burns are, broadly speaking, of two categories: (1) *Superficial*, i.e., those in which there is only partial skin destruction. (2) *Deep*, i.e., those in which there are areas of full-thickness loss.

In the first group rapid local regeneration of epithelium is possible. The objective in these cases is to permit this healing by preventing further tissue damage which would convert them into deep losses. Here it is pertinent to remember that devitalized and even normal tissue may be damaged by (a) too vigorous débridement, especially with ether; (b) the use of too strong antiseptics; and (c) infection.

In areas of full-thickness loss, regeneration can only take place from the sides of the wound. In extensive losses this epithelialization may be very slow and every day the wound is allowed to granulate means an increase in fibrosis with its sequelæ of contracture and loss of function. Therefore with this group, if the loss is of any considerable extent, the aim is to prepare the wound for the reception of a skin graft at the earliest possible moment. This involves measures to control infection and to achieve separation of sloughs.

Dressings.—At all dressings, gowns and masks should be worn by the staff and a mask by the patient. A rigid aseptic dressing technique is essential. The wounds and a wide area of surrounding skin should be gently but thoroughly cleansed with soap and water or 1 per cent. cetavlon, and then washed with saline. Blisters should be evacuated and all dead loose epithelium removed. An antibiotic cream spread on gauze should then be applied. This may contain penicillin, 500 units per g., or sulphanilamide 3 per cent. and sulphathiazole 3 per cent., in either case in a water soluble base. Over this is applied sterile cotton-wool and a firm crêpe pressure bandage, with the object of minimizing harmful œdema. Care should be taken to see that dressings are adequate in extent and so fixed as to preclude ingress of infection. It should be emphasized that frequent interference at this stage gains nothing and merely adds to the risk of infection. The initial dressing should therefore be left undisturbed for seven to ten days. By this time the full depth and area of the burn will usually be patent; superficial burns will be healed or obviously healing, and a dry dressing or further application of cream will be all that is required.

In *deeper burns*, sloughs will be present. The removal of these constitutes one of the most difficult problems we have to face. If small and localized, as they may be in burns due to molten metal or acid, a decision may be taken to excise them and apply a skin graft either forthwith or after a few days when healthy granulations appear. If the sloughs are more extensive, eusol dressings are instituted. A single layer of wide mesh gauze is placed next to the wound and over this thick gauze dressings wrung out in eusol. A layer of cellophane is then applied. The dressings are moistened with eusol four-hourly. The cellophane and outer gauze dressings are changed daily. By the end of three weeks, sloughs will usually have separated. The wound is then dusted daily with penicillin powder and saline packs applied. After a few days, provided the granulations look healthy and no hæmolytic streptococci or other virulent organisms are found on culture, grafting is undertaken.

In recent years attempts have been made to hasten the separation of slough by the application of 1 per cent. pyruvic acid or 1 per cent. phosphoric acid in starch paste. American workers have claimed considerable success. In my own hands the results have been variable but such as to warrant further trial. Early excision and grafting of deep burns has already been mentioned. This would appear to be the ideal, but the difficulty in practice is to decide the depth of destruction at an early stage.

BURNS IN SPECIAL AREAS

The hands.—These constitute a special problem. The chief consideration is to prevent stiffness which may occur as a result of œdema or prolonged immobilization. Œdema is minimized by elevation of the limb on a suitable splint. After the first dressing in seven days, saline baths are started and active movements of all joints encouraged. In deep burns early grafting is imperative.

The face, neck and perineum.—In these, adequate pressure and occlusive dressings are impracticable. The usual practice is merely to cover the areas with an anti-biotic cream on a thin dressing and to change this frequently. In perineal burns the patient is nursed on sterile sheets. Recently, Wallace has described the advantages of treating certain types of burn by keeping them dry and exposing them to light and atmospheric temperature. I have found the method of value in the treatment of burns of the perineum and buttocks in young children. The child is suspended by the feet, as in the treatment of fractured femur, and the burn is dusted with penicillin-sulphathiazole powder. A dry eschar forms and usually remains sterile, in contrast to the usual course of such burns.

LATE INFECTED BURNS

On admission, swabs are taken for culture and eusol or saline dressings instituted pending the bacteriological report. If penicillin-sensitive gram-positive organisms are found, penicillin powder is applied daily under the saline dressings or may be added to the saline in the strength of 10,000 units to the ounce. When penicillin-fast staphylococci or gram-negative organisms are present there is some evidence that some of the halogenated diamidines, notably dibromo-propamidine, are effective. Recent experience with a new antibiotic, polymixin, suggests that it may be of value in the treatment of pyocyanus infection. After seven to ten days' preparation in this way the granulations may be removed under general anaesthesia, and after a further three days, grafting may be undertaken.

J. S. TOUGH, M.B., F.R.C.S.ED.

NOTES AND QUERIES

Nocturnal Frequency after

Prostatectomy

QUERY.—I have a patient aged eighty-four, who in the early part of the summer underwent a wholly successful prostatectomy for enlargement of the prostate. Following the operation there was low-grade *B. coli* infection which responded satisfactorily to mandelic acid. The patient is now perfectly fit but he complains rather bitterly of nocturnal frequency. Could you recommend any form of treatment which might overcome this? Perhaps I should add that the patient drinks nothing after tea-time.

REPLY.—The continuance of nocturnal frequency of micturition after prostatectomy is

generally due to one or more of the following factors:—

(1) *Permanent preoperative renal changes* leading to an equalization of the volume secreted in periods of rest and activity. A small range of variability of the specific gravity of the urine would be an indication.

(2) The persistence of the *habit of waking for micturition*; the older the patient the more difficult it is for him to lose this habit. A mild sedative at bed-time often helps.

Both these factors are arguments in favour of early operation.

(3) *Infection.* The query does not state if urinary sterility was produced by the mandelic acid; if not, it would appear desirable to have

sensitivity tests done against the available antibiotics, and it may be found, for example, that a short course of streptomycin will prove effective.

(4) *Post-prostatectomy obstruction.* Unless the urinary stream is really good it would be wise to pass a full-sized metal bougie to test the calibre of the urethra and to treat accordingly.

(5) *An atonic bladder.* This only occurs when there has been long-continued chronic retention before operation, and it is more likely to cause nocturnal incontinence than frequency.

The factors of infection and obstruction are those which are most amenable to treatment, but the results of prostatectomy for benign enlargement can be so good that it would seem worth while returning the patient to his surgeon. Reassurance that all is well after thorough investigation will often improve matters greatly.

E. W. RICHES, M.C., M.S., F.R.C.S.

Treatment of Lupus Erythematosus

QUERY.—Could you inform me what treatment, if any, might prove useful in lupus erythematosus? I have recently taken over a case in a young man who has a patch on his nose and under his chin.

REPLY.—Before starting to treat a case of chronic discoid lupus erythematosus, streptococcal septic foci in the nasal pharynx should be eliminated, and the possibility of a tuberculous focus in the lung excluded. The patient should be warned against exposure to strong sunlight, and a protective cream such as 10 per cent. salol in yellow soft paraffin should be used on sunny days. A course of twelve weekly intramuscular injections of bismuth is often effective, and the course may be repeated after six weeks' rest. An oral preparation, such as "bistriplate", is said to be equally effective. If no improvement occurs with the bismuth courses a change should be made to gold injections, with the usual precautions against toxic effects. Locally, a 10 per cent. bismuth oxychloride ointment rubbed well in daily is very helpful, and in the more chronic cases with a dense scale, application of solid carbon dioxide snow for ten to fifteen seconds produces rapid improvement, a smooth white scar being left after the blistering heals. During bismuth and gold courses, nicotinic acid, 50 mg. b.d. by mouth, should be administered simultaneously.

P. D. C. KINMONT, M.D., M.R.C.P.

Treatment of Hypotension

QUERY.—What is the best drug for the treatment of hypotension, and is such treatment wise in a man who has had a stroke?

REPLY.—The first part of the question is best

answered by consideration of the etiology of the condition. Hypotension, that is a systolic pressure below 100 mm. Hg, occurs in the upright posture in two groups. The first consists of the adolescent of hyposthenic build, with inadequate splanchnic tone, in whom diminished venous return to the heart is accompanied by faintness, nausea and sweating. The second group of postural hypotension is limited to middle age, and occurs with impotence and absence of sweating; these patients have usually shown lesions in the central nervous system, such as tabes dorsalis or syringomyelia. Treatment by an abdominal support may be of help in the first group, who usually outgrow the symptom. Ephedrine, $\frac{1}{2}$ a grain (32 mg.) t.d.s., and amphetamine, 5 mg. in the morning, are of most use. Secondary hypotension is present in such conditions as shock, hæmorrhage, dehydration, diabetic ketosis, adrenal failure, coronary thrombosis, and certain acute infections. The treatment of the disease, if successful, is attended by readjustment of the blood pressure. Yet following coronary thrombosis, on account of the impaired left ventricle, although the systolic pressure may reach 120 mm. Hg or so, this may represent relative hypotension in an individual conditioned to a higher level, and accounts for the asthenia and undue fatigue which are frequent complaints. There is no adequate treatment for this; after the infarct is healed ephedrine may be used with caution.

With regard to the second part of the query: cerebral hæmorrhage and thrombosis are usually associated with hypertension and atheroma, less commonly with syphilis. The relative hypotension following the ictus is due to shock. In hæmorrhage this is a desirable condition, yet not in thrombosis. For, as is well known, thrombosis occurs particularly at night, or when the patient is exhausted and the blood pressure low. Theoretically therefore, assuming that most cerebral hæmorrhages will inevitably result in death, measures should be taken to raise the blood pressure and halt further clotting, when thrombosis has caused the stroke. Unfortunately, there is always the danger of hæmorrhage following thrombosis. Consequently, the avoidance of depletive measures, such as purgation and venesection, is desirable, but the blood pressure should be left to itself. Heparin is a more potent aid in checking thrombosis than is elevation of the blood pressure; but its use is only practicable in hospital.

RALPH KAUNTZE, M.B.E., M.D., M.R.C.P.

Nursing Tuberculosis

QUERY.—What is the normal practice in the larger London hospitals concerning the nursing of active tuberculosis by nurses in training? I

should be glad if the reply could deal with the question of Mantoux sensitivity.

REPLY.—Practice in different hospitals varies, and it is important to strike a balance between over-fastidious precautions and no precautions at all. The essential point of any scheme of control is to determine when the initial tuberculous infection takes place and what disturbance, if any, it causes. This is done by serial Mantoux testing.

All student nurses should be Mantoux tested and have their chests X-rayed before starting training. Those who are Mantoux positive, and who have therefore had their initial infection, can work in the tuberculosis wards immediately, provided the chest X-ray is normal; they should be X-rayed as a routine every six months or annually.

Nurses who are Mantoux negative, on the other hand, should work only in the general medical and surgical wards, and the tests should be repeated every three months until conversion takes place. Some hospitals repeat the test every two months, or even monthly, in order to determine as accurately as possible when initial infection takes place. At the time of conversion the nurse should be carefully questioned as to recent symptoms, if any; her weight should be checked and her erythrocyte sedimentation rate and chest X-ray done. If she is perfectly well and all these tests are negative she can be transferred to the tuberculosis wards; if, however, the result of any of these tests is adverse it is wise to discontinue training for three months

or until normal health has been restored. Thereafter she is treated in the same way as those who were Mantoux positive on arrival.

It should be mentioned that the introduction of B.C.G. vaccination for all student nurses is certain to modify the above practice considerably and render it largely obsolete.

N. LLOYD RUSBY, D.M., F.R.C.P.

Sedation for Infants

QUERY.—I would be grateful for information on the following points:—(1) Has the use of chloral hydrate resulted in the death of infants and young children? (that is to say, used in therapeutic doses). (2) What is an efficient substitute for use in a child aged fifteen months who is wakeful at night on account of teething pain?

REPLY.—(1) There is no evidence that chloral hydrate in therapeutic doses has resulted in the death of infants or young children. The margin of safety between the therapeutic and toxic doses appears to be very wide. Many paediatricians use it as the hypnotic of choice in doses of up to 1 grain (65 mg.) four or five times a day, for infants under a year.

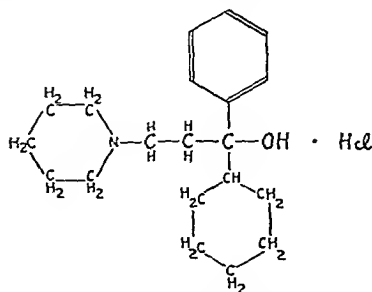
(2) Chloral has little or no analgesic property, and if the child is restless because of pain, aspirin in doses of 2½ to 5 grains (0.16 to 0.32 g.), which can be repeated at four-hourly intervals, would probably be a more efficient method for restlessness caused by teething.

R. E. BONHAM-CARTER, M.B., M.R.C.P.

PRACTICAL NOTES

Trihexyphenidyl ("Artane") in Parkinsonism

TRIHXYPHENIDYL ("artane": 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride) is a synthetic antispasmodic with the following structural formula:—



Chemical formula of trihexyphenidyl ("artane")

Its use at the Mayo Clinic in a group of 104 patients with idiopathic and postencephalitic Parkinsonism, spasmodic torticollis, facial spasm and allied conditions, is recorded by K. B. Corbin (*Journal of the American Medical Association*, October 8, 1949, 141, 377). The drug was given in initial dosage of 1 mg., four times daily, before meals and at bedtime; after several days increased to 2 mg. four times daily: average daily dose 8 mg. Of 69 patients with idiopathic Parkinsonism, 52 were benefited by the drug; 9 no improvement; 7 made worse. Of 17 patients with postencephalitic Parkinsonism, 12 received benefit, 3 no improvement, 1 made worse. In the spasmodic torticollis group (9 patients) subjective relief was obtained in 5. Four patients with facial spasm were treated: in this group there was initial marked improvement with recurrence of symptoms. It is stressed that the drug should be given in small doses initially and gradually in-

creased, so that the patient notices no side-reactions; these side-reactions include dryness of the mouth, lightheadedness and "jitteriness", and blurring of vision. Decreased rigidity was recorded in 75 per cent. of the series; reduced tremor in 50 per cent. The drug has a marked stimulative action, producing a sense of well-being. In a series of 117 patients with idiopathic, postencephalitic and arteriosclerotic Parkinsonism, L. J. Doshay and K. Constable (*Ibid.*, August 27, 1949, 140, 1317) noted the effectiveness of the drug in arteriosclerotic cases, in which smaller doses were needed than in the postencephalitic cases. These authors state that the toxic reactions are mild and that the drug has a marked cerebral-stimulating action; they conclude: "It recommends itself as the drug of choice in arteriosclerotic and idiopathic cases, and should be regularly tried in postencephalitic cases in which atropine or other forms of medication prove disturbing or ineffectual".

Sulphamethazine in Treatment of Urinary Infections

ACCORDING to A. M. Rutenburg (*Surgery*, August 1949, 26, 215), "sulphamethazine is a valuable addition to the list of chemotherapeutic agents for urinary infections due to gram-negative organisms because of its extremely low renal toxicity and its effectiveness, not only when used as the initial drug in the treatment, but also after others have failed to control the infection". This conclusion is based upon a series of 24 patients with urinary tract infections caused by gram-negative bacilli, treated with sulphamethazine: 4 to 6 g. daily given in divided doses. The daily intake of fluid was 2 to 2.5 litres, and 15 to 20 g. of sodium bicarbonate were also given daily in divided doses to keep the pH of the urine as far as possible towards the alkaline side. Nine of the cases were cured, whilst 10 were improved (i.e. cases of mixed infection in which some of the bacterial strains present were completely removed from the urine and the total bacterial count was markedly reduced). Of 11 cases which had previously failed to respond to treatment with sulphadiazine and sulphathiazole, nine responded favourably to sulphamethazine, and two patients who had failed to respond to streptomycin responded subsequently to sulphamethazine. Two patients in the series had toxic reactions: one, in whom a satisfactory fluid intake had not been maintained, developed a transient leucopenia; the other developed an allergic skin rash.

Streptomycin in Whooping-Cough

THE results obtained from the use of strepto-

mycin in 129 children with whooping-cough, 100 of whom were under one year of age, are reported by L. W. Wannamaker and his colleagues (*American Journal of Diseases of Children*, August 1949, 78, 201). The streptomycin was given in one of three ways:—(a) intranasally in the form of drops: 0.5 ml. of a solution containing 40,000 microgrammes of streptomycin per ml. of isotonic sodium chloride, introduced into each nostril thrice daily; (b) as an aerosol: 50,000 microgrammes in 1 ml. of isotonic sodium chloride thrice daily, i.e. 0.15 g. daily; (c) intramuscularly every three hours, the dose depending upon age: 50,000 microgrammes for infants under three months, 100,000 microgrammes for ages three months to one year, and 100,000 to 200,000 microgrammes for over one year. The results may be summarized as follows: Among 52 children treated intranasally, of whom three were severely ill, improvement was noted in 38. Among 35 children treated by aerosol, six of whom were severely ill, 28 were considered to be improved. Results were considered satisfactory in 22 of 26 children treated intramuscularly, of whom 7 were severely ill on admission. Of 31 children with whooping-cough who did not receive streptomycin, it is said: "we had the impression that the course of the illness was not so favourable as in those children who had been given streptomycin by aerosol mist or intramuscular injection". Given intranasally it was concluded that streptomycin was of little value. The final conclusion is that "streptomycin used as here described was not as effective in the treatment of whooping-cough as human hyperimmune serum". A subsequent report from the same hospital (K. E. Shepard *et al.*, *Ibid.*, p. 212), based upon a series of 69 cases of whooping-cough, 30 of which were under the age of one year, confirms the effects of streptomycin given simultaneously by aerosol and intramuscularly, and by aerosol alone. The conclusions drawn are that streptomycin appeared to have a favourable influence in children under the age of one year, and that there appeared to be no advantage in the combined administration by aerosol and intramuscularly when compared with aerosol or intramuscular injection alone.

The Treatment of Urinary Tuberculosis

FURTHER evidence in favour of the value of a combination of chaulmoogra oil and streptomycin in the treatment of urinary tuberculosis is provided by M. Schattyn (*Journal of Urology*, August 1949, 62, 457), who gives details of three cases treated in this way. The patients were hospitalized, but ambulatory. The chaulmoogra oil was given in the form of Moogrol

(Burroughs Wellcome), 1 ml. intramuscularly thrice daily, and the dosage of streptomycin was 0.25 g. every six hours (i.e. 1 g. every twenty-four hours). No toxic or allergic reactions to either drug were encountered. Tubercle bacilli were still present twelve and eight months respectively after treatment in two cases. It is concluded that "the medical treatment of urinary tuberculosis with small non-toxic doses of streptomycin in combination with the esters of chaulmoogra oil in the cases presented has resulted in remarkable clinical improvement and relief of the distressing symptoms of this disease for as long as 1 year following therapy... No evaluation of this therapy in early urinary tuberculosis can be deduced from the cases reported... The therapy used will be of definite value preoperatively, postoperatively, and in advanced inoperable cases of urinary tuberculosis".

Sodium Propionate in the Treatment of Pruritus Vulvæ

BENEFICIAL results are reported by A. M. Davids and A. Kurtin (*American Journal of Obstetrics and Gynecology*, August 1949, 58, 397) from the use of sodium propionate in the treatment of pruritus vulvæ. A 15 per cent. sodium propionate ointment, with a vanishing cream base containing a wetting agent, was rubbed into the vulva and perianal skin two or three times daily. In some cases vaginal suppositories of 10 per cent. sodium propionate were also used, whilst patients with a vaginal discharge were instructed to use a 5 per cent. sodium propionate douche night and morning. Of 15 patients with pruritus vulvæ of one month's to three years' duration, associated with diabetes mellitus, eight obtained complete relief within a week, whilst the remainder required treatment for two to four weeks for "complete restoration to normal". Eight patients with mycotic vulvovaginitis were treated by means of the ointment and suppositories, and seven of them obtained complete relief within one to three weeks. Of 22 cases of "menopausal or atrophic vulvitis", aged fifty to seventy-seven years, only three still complained of irritation after two months of treatment. Most of them began to feel better after a few days, but it was two to eight weeks before the pruritus disappeared completely in this group.

Oral Bismuth in Dermatology

Using sodium bismuth triglycollamate, 1 g. of which contains the equivalent of 0.138 g. of metallic bismuth, in doses of one tablet (equivalent of 75 mg. metallic bismuth) orally thrice daily for three days and then two tablets

thrice daily, T. H. Miller and J. R. Delaney (*Archives of Dermatology and Syphilology*, August 1949, 60, 196) report the results obtained in 46 patients: 18 with various types of verrucae; 3 with condyloma acuminatum; 12 with lupus erythematosus; 11 with lichen planus; 3 with scleroderma. Toxic reactions were minimal and consisted of mild gingivitis. Of the verrucae, the juvenile flat warts responded better than verruca vulgaris, and 5 of 6 cases were completely cleared within two to four weeks. The patients with condyloma acuminatum "attained approximately 90 per cent. involution of the lesions after seven, sixteen and twenty weeks of treatment". The disseminated type of lupus erythematosus responded better than the chronic discoid type. All the cases of lichen planus responded satisfactorily, 7 of the 8 patients with generalized lesions showing complete involution after two to eight weeks' treatment. The two patients with scleroderma showed "moderate clinical improvement".

Human Requirements of Vitamin A

IN discussing the recent Medical Research Council report on "vitamin A requirement of human adults", M. W. Grant (*Nature*, London, August 6, 1949, 164, 212) stresses the particular difficulties that arise in assessing the requirements of vitamin A because of the fact that it is normally obtained partly in the preformed state and partly as a precursor—carotene. The final recommendation of the report is "a round figure of 2,500 I.U. vitamin A daily for a normal human adult". In calculating the vitamin potency of a mixed diet it is recommended that the total carotene value of root vegetables should be divided by 4, and that of green vegetables by 2.5, and that this figure should be added to the value of preformed vitamin A. A plea is made for giving estimates of requirements of vitamin A in terms of vitamin A *per se*, whilst in the case of reports of food consumption it is suggested that the quantities of vitamin A and of carotene should be given separately, "the estimation of the resultant vitamin A potency being given as an additional figure, together with a description of how it was obtained".

Gammexane in the Treatment of Head Lice

ON the basis of experience in Malaya, a "simple, rapid and inexpensive" form of treatment of head lice is outlined by J. R. Busvine and J. A. Reid (*Medical Journal of Malaya*, June 1949, 3, 232). The preparation used was 0.2 per cent. gamma BHC (gamma isomer of benzene hexachloride) in coconut oil solution, prepared by adding "one part of 'gammexane' concentrate

creased, so that the patient notices no side-reactions; these side-reactions include dryness of the mouth, lightheadedness and "jitteriness", and blurring of vision. Decreased rigidity was recorded in 75 per cent. of the series; reduced tremor in 50 per cent. The drug has a marked stimulative action, producing a sense of well-being. In a series of 117 patients with idiopathic, postencephalitic and arteriosclerotic Parkinsonism, L. J. Doshay and K. Constable (*Ibid.*, August 27, 1949, 140, 1317) noted the effectiveness of the drug in arteriosclerotic cases, in which smaller doses were needed than in the postencephalitic cases. These authors state that the toxic reactions are mild and that the drug has a marked cerebral-stimulating action; they conclude: "It recommends itself as the drug of choice in arteriosclerotic and idiopathic cases, and should be regularly tried in postencephalitic cases in which atropine or other forms of medication prove disturbing or ineffectual".

Sulphamethazine in Treatment of Urinary Infections

ACCORDING to A. M. Rutenburg (*Surgery*, August 1949, 26, 215), "sulphamethazine is a valuable addition to the list of chemotherapeutic agents for urinary infections due to gram-negative organisms because of its extremely low renal toxicity and its effectiveness, not only when used as the initial drug in the treatment, but also after others have failed to control the infection". This conclusion is based upon a series of 24 patients with urinary tract infections caused by gram-negative bacilli, treated with sulphamethazine: 4 to 6 g. daily given in divided doses. The daily intake of fluid was 2 to 2.5 litres, and 15 to 20 g. of sodium bicarbonate were also given daily in divided doses to keep the pH of the urine as far as possible towards the alkaline side. Nine of the cases were cured, whilst 10 were improved (i.e. cases of mixed infection in which some of the bacterial strains present were completely removed from the urine and the total bacterial count was markedly reduced). Of 11 cases which had previously failed to respond to treatment with sulphadiazine and sulphathiazole, nine responded favourably to sulphamethazine, and two patients who had failed to respond to streptomycin responded subsequently to sulphamethazine. Two patients in the series had toxic reactions: one, in whom a satisfactory fluid intake had not been maintained, developed a transient leucopenia; the other developed an allergic skin rash.

Streptomycin in Whooping-Cough

THE results obtained from the use of strepto-

mycin in 129 children with whooping-cough, 100 of whom were under one year of age, are reported by L. W. Wannamaker and his colleagues (*American Journal of Diseases of Children*, August 1949, 78, 201). The streptomycin was given in one of three ways:—(a) intranasally in the form of drops: 0.5 ml. of a solution containing 40,000 microgrammes of streptomycin per ml. of isotonic sodium chloride, introduced into each nostril thrice daily; (b) as an aerosol: 50,000 microgrammes in 1 ml. of isotonic sodium chloride thrice daily, i.e. 0.15 g. daily; (c) intramuscularly every three hours, the dose depending upon age: 50,000 microgrammes for infants under three months, 100,000 microgrammes for ages three months to one year, and 100,000 to 200,000 microgrammes for over one year. The results may be summarized as follows: Among 52 children treated intranasally, of whom three were severely ill, improvement was noted in 38. Among 35 children treated by aerosol, six of whom were severely ill, 28 were considered to be improved. Results were considered satisfactory in 22 of 26 children treated intramuscularly, of whom 7 were severely ill on admission. Of 31 children with whooping-cough who did not receive streptomycin, it is said: "we had the impression that the course of the illness was not so favourable as in those children who had been given streptomycin by aerosol mist or intramuscular injection". Given intranasally it was concluded that streptomycin was of little value. The final conclusion is that "streptomycin used as here described was not as effective in the treatment of whooping-cough as human hyperimmune serum". A subsequent report from the same hospital (K. E. Shepard *et al.*, *Ibid.*, p. 212), based upon a series of 65 cases of whooping-cough, 30 of which were under the age of one year, confirms the effects of streptomycin given simultaneously by aerosol and intramuscularly, and by aerosol alone. The conclusions drawn are that streptomycin appeared to have a favourable influence in children under the age of one year, and that there appeared to be no advantage in the combined administration by aerosol and intramuscularly when compared with aerosol or intramuscular injection alone.

The Treatment of Urinary Tuberculosis

FURTHER evidence in favour of the value of a combination of chaulmoogra oil and streptomycin in the treatment of urinary tuberculosis is provided by M. Schittyn (*Journal of Urology*, August 1949, 62, 457), who gives details of three cases treated in this way. The patients were hospitalized, but ambulatory. The chaulmoogra oil was given in the form of Moogrol

(Burroughs Wellcome), 1 ml. intramuscularly thrice daily, and the dosage of streptomycin was 0.25 g. every six hours (i.e. 1 g. every twenty-four hours). No toxic or allergic reactions to either drug were encountered. Tubercle bacilli were still present twelve and eight months respectively after treatment in two cases. It is concluded that "the medical treatment of urinary tuberculosis with small non-toxic doses of streptomycin in combination with the esters of chaulmoogra oil in the cases presented has resulted in remarkable clinical improvement and relief of the distressing symptoms of this disease for as long as 1 year following therapy . . . No evaluation of this therapy in early urinary tuberculosis can be deduced from the cases reported. . . The therapy used will be of definite value preoperatively, postoperatively, and in advanced inoperable cases of urinary tuberculosis".

Sodium Propionate in the Treatment of Pruritus Vulvæ

BENEFICIAL results are reported by A. M. Davids and A. Kurtin (*American Journal of Obstetrics and Gynecology*, August 1949, 58, 397) from the use of sodium propionate in the treatment of pruritus vulvæ. A 15 per cent. sodium propionate ointment, with a vanishing cream base containing a wetting agent, was rubbed into the vulva and perianal skin two or three times daily. In some cases vaginal suppositories of 10 per cent. sodium propionate were also used, whilst patients with a vaginal discharge were instructed to use a 5 per cent. sodium propionate douche night and morning. Of 15 patients with pruritus vulvæ of one month's to three years' duration, associated with diabetes mellitus, eight obtained complete relief within a week, whilst the remainder required treatment for two to four weeks for "complete restoration to normal". Eight patients with mycotic vulvovaginitis were treated by means of the ointment and suppositories, and seven of them obtained complete relief within one to three weeks. Of 22 cases of "menopausal or atrophic vulvitis", aged fifty to seventy-seven years, only three still complained of irritation after two months of treatment. Most of them began to feel better after a few days, but it was two to eight weeks before the pruritus disappeared completely in this group.

Oral Bismuth in Dermatology

USING sodium bismuth triglycollamate, 1 g. of which contains the equivalent of 0.138 g. of metallic bismuth, in doses of one tablet (equivalent of 75 mg. metallic bismuth) orally thrice daily for three days and then two tablets

thrice daily, T. H. Miller and J. R. Delaney (*Archives of Dermatology and Syphilology*, August 1949, 60, 196) report the results obtained in 46 patients: 18 with various types of verrucæ; 3 with condyloma acuminatum; 12 with lupus erythematosus; 11 with lichen planus; 3 with scleroderma. Toxic reactions were minimal and consisted of mild gingivitis. Of the verrucæ, the juvenile flat warts responded better than verruca vulgaris, and 5 of 6 cases were completely cleared within two to four weeks. The patients with condyloma acuminatum "attained approximately 90 per cent. involution of the lesions after seven, sixteen and twenty weeks of treatment". The disseminated type of lupus erythematosus responded better than the chronic discoid type. All the cases of lichen planus responded satisfactorily, 7 of the 8 patients with generalized lesions showing complete involution after two to eight weeks' treatment. The two patients with scleroderma showed "moderate clinical improvement".

Human Requirements of Vitamin A

IN discussing the recent Medical Research Council report on "vitamin A requirement of human adults", M. W. Grant (*Nature*, London, August 6, 1949, 164, 212) stresses the particular difficulties that arise in assessing the requirements of vitamin A because of the fact that it is normally obtained partly in the preformed state and partly as a precursor—carotene. The final recommendation of the report is "a round figure of 2,500 I.U. vitamin A daily for a normal human adult". In calculating the vitamin potency of a mixed diet it is recommended that the total carotene value of root vegetables should be divided by 4, and that of green vegetables by 2.5, and that this figure should be added to the value of preformed vitamin A. A plea is made for giving estimates of requirements of vitamin A in terms of vitamin A *per se*, whilst in the case of reports of food consumption it is suggested that the quantities of vitamin A and of carotene should be given separately, "the estimation of the resultant vitamin A potency being given as an additional figure, together with a description of how it was obtained".

Gammexane in the Treatment of Head Lice

ON the basis of experience in Malaya, a "simple, rapid and inexpensive" form of treatment of head lice is outlined by J. R. Busvine and J. A. Reid (*Medical Journal of Malaya*, June 1949, 3, 232). The preparation used was 0.2 per cent. gamma BHC (gamma isomer of benzene hexachloride) in coconut oil solution, prepared by adding "one part of 'gammexane' concentrate

LG 140 (obtainable from Imperial Chemical Industries Ltd.) to 50 parts of coconut oil and stirring. The concentrate LG 140 is an organic solvent containing 10 per cent. of a refined grade of gamma BHC which is largely without the rather disagreeable smell of crude samples of BHC". To prevent accidental ingestion of the medicated oil it is recommended that colouring matter should be added, e.g. 0.1 g. per gallon of the I.C.I. dye known as "waxoline blue CBS". The best way of incorporating this dye is to dissolve it first in a few millilitres of chloroform and then add the concentrated solution to the oil. Treatment consisted of applying 10 ml. of the medicated oil to the hair by pipette and distributing it as evenly as possible by rubbing with the hand. Of the 30 children treated in this way, all were free of lice one week later, whereas of 30 children treated with 4 per cent. DDT in oil, only 20 were free of lice one week after treatment.

Xiphosternal Crunch

XIPHOSTERNAL crunch is defined by L. Schwab, G. L. Smiley and W. P. Meyn (*Annals of Internal Medicine*, August, 1949, 31, 228) as "a systolic sound of a crunching or spitting nature heard best at a point immediately to the left and above the xiphoid process, in the absence of signs of organic heart disease". In a series of 3,224 "Army separates" it was found in 106 individuals (i.e., an incidence of 3.3 per cent.). The only correlation with physical type was that some degree of funnel chest was found in 25 per cent. of those showing the crunch. This may be significant, as in a series of 46,705 persons Ochsner only found an incidence of 0.059 per cent. of severe degrees of funnel chest. In 82 per cent. of the cases the sound was sharply localized just to the left and above the xiphoid process and it was not heard more than one inch from this spot. The sound did not vary with respiration in 75 per cent. of cases; in the remainder it increased in intensity during expiration. The suggestion is advanced that "the sound is produced by the cardiac thrust against the chest wall, leading to movement of the left seventh costal cartilage at the point of its articulation with the sternum and the xiphoid process".

Hazards of Fluorescent Lighting

IN reporting five cases of cutaneous irritation due to exposure to fluorescent lighting occurring among operatives in the penicillin filling room of an American pharmaceutical organization, R. R. Bresler (*Journal of the American Medical Association*, August 27, 1949, 140, 1334) draws attention to "the possibility that undesirable cutaneous reactions may follow prolonged exposure to fluorescent lighting at relatively

short working distances". The operatives complained of redness, dryness, and occasional itching of the skin on the arms and exposed parts of the neck and front of the chest. Examination revealed erythematous areas with dryness and moderate desquamation. The filling room was illuminated by ordinary fluorescent tubes which were placed within 10 to 12 inches of the operators. When a $\frac{1}{4}$ -inch (0.6 cm.) thick all-round plate-glass shield was placed round the tubes the erythema disappeared and did not recur. Reference is made to two other cases of dermatitis from exposure to fluorescent lighting (A. P. R. James, *Archives of Dermatology and Syphilology*, August 1941, 44, 256). In one of these the patient worked at a desk with a day-light fluorescent tube three feet above the desk; the other was a woman who worked in an office lit by four 40-watt daylight tubes placed at about 8 feet above her. It is suggested that "with the increasing use of fluorescent lighting, it is only logical to expect an increase in the number of persons who may react unfavourably to it".

Nicotine Absorbed in Smoking

USING a biological means of estimation (i.e., the effect on the blood pressure of the spinal cat) H. W. Ling and C. B. Wynn Parry (*British Journal of Pharmacology*, September 1949, 4, 313) found the amount of nicotine deposited in the smoke from well-known brands of cigarettes to range from 0.72 to 1.2 mg. per cigarette, with a mean of 0.92 mg. In the case of cigars (weight about 5 g.) the corresponding figures were 3.6 to 7.9 mg. per cigar, or 0.7 to 1.6 mg. per g. tobacco. For pipe tobacco the nicotine content ranged from 2 to 3 mg. per g. tobacco. This represents the amount of nicotine entering the mouth of the smoker. The proportion absorbed depends upon the extent to which the smoke is inhaled. Most of the nicotine entering the alveoli is absorbed, but even in the case of non-inhalers it is estimated that slightly less than half the nicotine is absorbed, i.e., 0.9 mg. nicotine enters the mouth in smoking the amount absorbed without inhaling is 0.4 mg. or less, per cigarette.

Relief of Toothache

THE following formula for toothache drops is taken from a review in *Pharmacy International* 1949, 3, 16 (quoted by *Manufacturing Chemist* August 1949, 20, 398):—

Clove oil	15 ml.
Phenol, liquid	90 ml.
Glycerin	180 ml.
Amaranth solution (7 per cent.) sufficient to colour.	

For the temporary relief of toothache it is recommended that a small pledget of cotton wet with this preparation be placed in the socket and then covered with dry cotton.

REVIEWS OF BOOKS

Modern Practice in Anæsthesia. EDITED BY FRANKIS T. EVANS, M.B., B.S., F.F.A.R.C.S., D.A. London: Butterworth & Co. (Publishers) Ltd., 1949. Pp. xx, 566 and 40. Figures 227. Price 50s.

THIS textbook will for long be a source of pride to British anæsthetists. The book really begins with the noteworthy chapter by Blair Gould on the volatile narcotics and anæsthetics. Then follow excellent accounts of apparatus, the preparation of the patient and the administration of rectal and intravenous drugs. An otherwise helpful chapter on the preparation of the patient is marred by a liberal spattering of diagrams consisting of whirlpools of arrows which make the eye giddy and the mind but tired. Their educational value is dubious. Curariform drugs receive very adequate treatment at the hands of Low and Maureen Young. In this chapter erythroidine and myanesis are included, but the book evidently went to press before clinical reports of Cro and "flaxedil" were available. The curare-like action of quinine derivatives is given but passing mention, although quinine methochloride served as an effective substitute for curare in Denmark during the war, and reports of its use in anæsthesia came from there and from the United States. Massey Dawkins writes a competent chapter on paravertebral and epidural blocks, drawing on his own experiences of these methods. The editor himself deals with spinal techniques. The chapter on local analgesia by Dodd is excellent so far as it goes, although techniques which involve such obviously surgical procedures as infiltrating the abdominal viscera seem a little out of place in a textbook for anæsthetists. Perhaps in future editions the whole of the body will be dealt with in as great detail as the abdomen and the brachial plexus are in this one. Dodd condemns nitrous oxide and oxygen as a supplement to local analgesia; his opinion will be confirmed by most surgeons who habitually operate under block anæsthesia. The second half of the book contains an assortment of chapters: anæsthetic emergencies, blood transfusion and fluid replacement, and anæsthesia for thoracic, neurosurgical, plastic, thyroid, and rectal operations. Obstetric and dental anæsthesia are given ample treatment, as is anæsthesia in old age and in shock.

The authors, perhaps naturally, stress the methods and views currently obtaining in London, but their outlook is broad and their reference wide. There is no more complete survey of clinical anæsthesia in one volume.

Aviation Medicine. Its Theory and Application. BY KENNETH G. BERGIN, M.D., D.P.H., A.F.R.A.C.S. Bristol: John Wright & Sons Ltd., 1949. Pp. xiv and 447. Figures 131. Price 35s.

THE rapid development of civil aviation is making it incumbent for an increasing number of practitioners to be able to advise their patients as to their medical fitness for flying. To be able to do this intelligently requires a modicum of knowledge of the physiological considerations involved. This particular field of medical research has undergone such dramatic changes during the last ten years that it is well nigh impossible for anyone but the interested expert to keep pace with it. The result is that many practitioners, aware of their ignorance, either refrain from giving advice on the subject or alternatively play for safety and advise their patient to travel by surface routes. This unfortunate state of affairs has now been rectified by Dr. Bergin who, on the basis of personal experience as a pilot and as an R.A.F. and B.O.A.C. medical officer, has written a book which is not only intensely practical but also gives an admirably lucid interpretation of all the salient modern research work on the subject. One section, devoted to "physiological considerations", deals with the problems of vision, hearing, speed and acceleration, equilibrium, pressurization, noise and vibration, and the like, and explains them in terms which the uninitiated will have no difficulty in understanding. Another section deals fully with medical considerations, whilst yet another deals with psychological considerations. There is a valuable section on epidemiology and air travel, and the book concludes with a useful series of appendices giving details concerning international certificates of inoculation and vaccination, and yellow fever inoculation centres. Two minor criticisms must be made. Is the etiology of "postural œdema" as simple and straightforward as it is made out to be here? There is an air of unreality about the statement that "streptomycin is also contraindicated for the pilot". Surely, one of the first principles of medicine is that an individual who requires streptomycin is one who must be confined to bed, and even to suggest that a pilot may fly a machine when he is in this state is unfortunate. These, however, are exceptions in an otherwise excellent book which will be welcomed by all who have to deal with the medical aspects of flying, and there are few doctors these days who do not fall into this category.

Bedside Diagnosis. By CHARLES MACKAY SEWARD, M.D., F.R.C.P.ED. Foreward by SIR HENRY COHEN, M.D., F.R.C.P. Edinburgh: E. & S. Livingstone Ltd., 1949. Pp. vii and 372. Illustrated. Price 17s. 6d.

Dr. Seward takes the common symptoms and signs—head pains, stomach pains, shortness of breath, cough, tachycardia, anaemia, and loss of weight, and discusses them with a view to making a diagnosis at the bedside of the patient. Each chapter is preceded by a synopsis of the causes of the symptom, and there then follows a short account of its physiology, his general considerations regarding pain being particularly good in this respect. The symptom is then discussed in relation to the diseases which may cause it, and mention is made of associated symptoms and additional aids to diagnosis. Dr. Seward rightly stresses how often psychological disturbances produce physical symptoms, and he emphasizes that the management of such cases is generally well within the province of the general physician. This is an excellent book.

Clinical Auscultation of the Heart. By SAMUEL A. LEVINE, M.D., and W. PROCTOR HARVEY, M.D. Philadelphia and London: W. B. Saunders Company, 1949. Pp. viii and 327. Figures 286. Price 32s. 6d.

It is a sign of the times that this admirable book on auscultation should have come from the United States, the home of laboratory and mechanized medicine. It is presumably a reaction to the over-swing of the pendulum which has always been more marked on the other side of the Atlantic. The authors will strike a responsive chord in the hearts of many physicians in Great Britain with their statement that "it is imperative to derive all possible help from such an inexpensive and expedient tool as the stethoscope". The book is comprehensive without ever becoming too detailed. It is divided into four sections, dealing with heart sounds, cardiac irregularities, cardiac murmurs, and miscellaneous auscultatory findings, all exceptionally well illustrated with a series of excellent phonocardiograms and electrocardiograms. These are used merely to demonstrate the various types of murmurs which can be heard by auscultation, and care is taken to point out that in the general run of clinical cardiology phonocardiograms are not essential. As a means of teaching clinical auscultation, however, they subserve a most useful function. This is a book which should be in the hands of every senior medical student and all concerned with the teaching of medicine.

The Principals of Chiropody. By JOHN H. HANBY, F.Ch.S., and H. F. WALKER, F.Ch.S. London: Baillière, Tindall & Cox, 1949. Pp. ix and 383. Figures 129. Price 21s.

THE authors of this new textbook are to be congratulated on the production of an excellent book, well classified and illustrated, which is certain to become a volume to which every student of chiropody will turn for guidance in his professional studies. The names of Hanby and Walker, associated as they are with the leading chiropody school in this country, are an assurance to the reader that the book is based on wide and extensive practical experience. The earlier chapters deal in some detail with the anatomy and physiology of the foot and provide the student with a sound basis for his later clinical studies. An excellent and instructive chapter on the function of the foot is included. In each clinical section the authors have been especially careful to explain in simple language the principles on which diagnosis and treatment are based. An attractive chapter deals with those changes in the shoe which are indicative of abnormal strain on the foot. There is much to learn from this delightful book, which can be warmly recommended to the reader.

Varicose Veins. By R. ROWDEN FOOTE, M.R.C.S., D.Obst. R.C.O.G. London: Butterworth & Co. (Publishers) Ltd., 1949. Pp. xii and 214. Figures 205 and 3 coloured plates. Price 32s. 6d.

THE surgical perspective is sadly warped by the attraction of the rare and the bizarre case, and by the drama of the highly technical and highly useless operative *tour de force*. The treatment of common injuries and of common infections, particularly of the hand, of minor fractures, haemorrhoids, herniae, and varicose veins far outweighs in importance the stunts of the super-specialist, yet, because they have no box-office appeal, these useful procedures are handed over to juniors, often without supervision. A visit to any surgical clinic from Secunderabad to Seattle provides the same experience: in theatre A an eminent professor surrounded by admiring yes-men is performing some heroic and useless *spécialité de la maison* on a moribund patient; in theatre B a man who hopes one day to move into theatre A is wrecking an inguinal canal in the attempt to devise yet another modification of Bassini's operation; in theatre C a junior ignorant of surgical technique and of anatomy has pulled out an inch of the internal saphenous vein from a small gory hole much as a thrush pulls an inch of worm from a muddy

lawn, and is proceeding to ligature it well below its junction with the femoral vein.

Mr. Rowden Foote has devoted himself to the study of varicose veins, their etiology, their symptoms, and their complications and their treatment, and in this book he has set down his views with admirable clearness, helped still further by a wealth of excellent illustrations. He mentions everything, even the many tests which look so nice on paper but which surgeons cease to employ as soon as they know their job, but he keeps a sense of proportion; the description of the anatomy and variations of the superficial veins at the saphenous opening and of the technique of high saphenous ligature, could not be bettered. The only possible criticism is that the author, although his trend is towards surgery, still dabbles somewhat largely in chemical sclerosis, a method of treatment that many would like to see removed from the field of therapeutics. This book can be recommended with confidence to any reader seeking reliable information on the treatment of varicose veins.

Elements of Food Biochemistry. BY WILLIAM H. PETERSON, PH.D., JOHN T. SKINNER, PH.D., and FRANK M. STRONG, PH.D. London: Staples Press Ltd., 1949. Pp. xi and 259. Price 21s.

This book gives a complete survey of the chemistry and physiology of foods and can be recommended. Tables of the economic importance of carbohydrates, fats and proteins add interest to these chapters. In chapter III the authors show how easy it is to calculate that pH 5.1 is 32 times as acid as pH 6.6 and how buffer solutions work. The complex changes occurring in the breakdown of glucose, as also the oxidative changes in cells, are made very clear in the short space available. Amongst the many illustrations are crystals of vitamins and enzymes. Food analyses, including mineral content, trace elements and vitamins conclude the book. There is no index.

NEW EDITIONS

THE doyen of Canadian medicine has added to his many contributions to medicine by bringing out a second edition of his admirable book on symptomatology, *Symptoms in Diagnosis*, by Jonathan Campbell Meakins, C.B.E., M.D., D.Sc., LL.D. (Baillière, Tindall and Cox, 42s.). In preparing this edition he has called upon his younger colleagues for assistance in preparing the chapters dealing with the eyes, the ear, nose and throat, the nervous system, and psychiatry. As an attempt to correlate symptoms with physiological processes, this book is an outstanding contribution to clinical medicine.

THE second edition of *Geriatric Medicine*, by Edward J. Stieglitz, M.D., M.S., F.A.C.P. (W. B. Saunders Company, 60s.) has appeared within six years of the first publication. Under the editorship of Dr. Stieglitz a considerable number of American specialists have contributed chapters. The parts written by Dr. Stieglitz, who is convinced that geriatric medicine can only advance by the study of gerontology and by appreciation of the sociological aspect, are particularly interesting and sound. This book will prove valuable to those specialists in this branch of medicine and can, with profit, be consulted by any practitioner who wants the fullest information on the signs, symptoms and treatment of diseases in the aged.

CAREFUL revision and some rewriting have been carried out in the preparation of the thirtieth edition of *Gray's Anatomy*, edited by T. B. Johnston, C.B.E., M.D., and J. Willis, M.D., M.S. (Longmans, Green and Co., 84s.), and a number of new illustrations have been added and many replaced. This work is such a well-established classic that any detailed comment is unnecessary.

THE third edition of Dr. Tramer's world famous book *Lehrbuch der Allgemeinen Kinderpsychiatrie* (Benno Schwabe, Basle, Sw. frs. 38) is welcome. Several subjects have been treated more fully in the eighteen months that have elapsed since the appearance of the last edition, and the chapter on treatment has been rewritten. The book is essential for those engaged in this specialty, and an English translation would be most valuable.

Pathology of the Nervous System, by J. HENRY BIGGART, C.B.E., M.D., D.Sc., in its second edition (E. & S. Livingstone Ltd., 21s.) has been largely rewritten and a number of new illustrations added. Although written primarily for students preparing for the Diploma of Psychiatry, the practitioner will find this work a valuable addition to his library.

Hematology, by Willis M. Fowler, M.D., in its second edition (Cassel and Co. Ltd., 44s.) contains many new advances: folic acid in the treatment of pernicious anaemia and sprue; urethane in leukaemia; nitrogen mustard in lymphomas and other conditions; radiophosphorus in polycythæmia and leukaemia, and complete revision on the chapter on "transfusion of whole blood and blood derivatives".

Food Inspection Notes, by H. Hill, F.R.SAN.I., F.S.I.A., A.M.I.S.E., and F. Dodsworth, M.R.SAN.I., M.S.I.A., in its third edition (H. K. Lewis & Co. Ltd., 7s. 6d.) contains among other useful information a chapter on food poisoning.

NOTES AND PREPARATIONS

NEW PREPARATIONS

ANTISTIN CREAM AND OINTMENT, each containing 2 per cent. antistin, have been prepared for the local treatment of allergic skin disorders, either alone or in conjunction with oral antistin therapy. The ointment is stated to be suitable for dry and scaly conditions, whereas the cream with a water-miscible base is more generally preferable, especially in exposed areas. They are supplied in tubes of 20 g. (Ciba Laboratories Ltd., Horsham, Sussex.)

AUREOMYCIN (Lederle).—Supplies of this antibiotic are now available on prescription for urgent cases. Aureomyein (Lederle) is issued in vials of 16 capsules of 250 mg. for oral use, and in vials of 25 mg. with dropper for ophthalmic use. (Lederle Laboratories Division, Cyanamid Products Ltd., Brettenham House, London, W.C.2.)

INJECTION SOLUTION B.A.L. (dimercaprol or 2,3 dimercaptopropanol), a 5 per cent. solution in arachis oil with 10 per cent. of benzyl benzoate, for intramuscular injection, is issued in ampoules of 2 ml., in boxes of 6, 12 and 100. (Allen & Hanburys Ltd., London, E.C.2.)

LACTALUMINA COMPOUND (CROOKES).—Each compound tablet contains aluminium hydroxide 2 grains, magnesium trisilicate 2 grains, magnesium oxide $\frac{1}{2}$ grain, and papain $\frac{1}{2}$ grain. The tablets have been prepared for the use of patients with dyspepsia or peptic ulcer. Supplied in cartons of 12 packet packings, each containing 12 tablets. (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

OPTALIDON, an analgesic which is stated to relieve pain without causing drowsiness or stupor, is now again available. It is issued in tubes of 10 tablets, and bottles of 25, 100 and 250. (Sandoz Products Ltd., 134 Wigmore Street, London, W.1.)

LEAD POISONING IN BABIES DUE TO NIPPLE SHIELDS

A NOTE from the Ministry of Health draws attention to the occurrence of a number of cases of lead encephalopathy in babies resulting from the use of lead nipple shields by their mothers. Immediate administrative action is being taken to discourage the prescription and use of lead nipple shields under Part IV of the National Health Service Act, 1946, and these shields will be excluded from the list of appliances in Part I of the Third Schedule.

MEDICAL FILM

A FILM illustrating "The Technique of Sub-

cutaneous Hormone Implantation", demonstrated by G. I. Swyer, D.M., M.R.C.P., has been produced for Roussel Laboratories Ltd., by Brian Stanford, M.R.C.S., D.M.R., F.R.P.S. The film (16 mm. silent, in colour, running 7 minutes), designed for teachers of obstetrics and endocrinology for illustrating lectures, may be obtained free on application. (Roussel Laboratories Ltd., 95 Great Portland Street, London, W.1.)

PUBLICATIONS

Diets for Sick Children has been prepared by the Hospital for Sick Children, Great Ormond Street. The pamphlet deals first with the general preparation of diets, and then with diets for specific conditions. Some useful recipes are included. (The Dietitian, Hospital for Sick Children, Great Ormond Street, London, W.C.1, price 1s.)

Lewis's Diet Charts.—This set of 25 diet tables is designed for the use of physicians for handing to patients after consultation, modified to suit individual requirements. The subjects covered are: allergy, dyspepsia, peptic ulcer convalescence, ketosis, gout, obesity, heart, kidney and nervous diseases, sodium elimination, fever, gravel, chronic diarrhoea, tuberculosis, rheumatism, constipation, anaemia, and convalescence. A specimen packet of 4 copies of each chart and a twelve page booklet "Notes to Lewis's Diet Charts", price 7s.; 100 charts, assorted to suit individuals requirements, price 6s.; smaller quantities 1s. per dozen, and the booklet 1s. net; plus postage. (H. K. Lewis & Co., Ltd., 136 Gower Street, London, W.C.1.)

Catalogue of an Exhibition of Books, Manuscripts and Relics, Commemorating the Bicentenary of Edward Jenner, 17 May, 1749—26 January, 1823, is published by the Oxford University Press for the Trustees of the Wellcome Historical Medical Museum. A brief biography of Edward Jenner and his work is given in the introduction, which is followed by an account of his work on small-pox inoculation. (Oxford University Press, 2s.)

Entry into Practice, published by the Medical Practitioners' Union, deals with the problems of entering general medical practice and consultant practice under the National Health Service. Some constructive suggestions are made. (Medical Practitioners' Union, 55-6 Russell Square, London, W.C.1.)

The contents of the December issue, which will contain a symposium on "Respiratory Diseases", will be found on page lxxviii at the end of the advertisement section.

THE PRACTITIONER

No. 978

DECEMBER 1949

Volume 163

A MODERN VIEWPOINT ON INFLUENZA

By C. H. STUART-HARRIS, M.D., F.R.C.P.

Professor of Medicine, University of Sheffield; Physician, United Sheffield Hospitals.

INFLUENZA, as its name implies, has historically been regarded as a mysterious disease. In the past, this reputation was doubtless gained by reason of its sudden appearances, rapid spread, and tendency to change from a mild to a lethal disease of dreaded proportions. To-day, some at least of the mystery has been unveiled, but a host of unsolved problems remains to perplex and challenge us. The modern observer must therefore admit a viewpoint based upon imperfect knowledge, whether he be primarily interested in epidemiology, immunity or even diagnosis; the latter remains a difficulty because of the confused tangle of the common maladies of the respiratory tract, amongst which influenza constitutes but one member.

ETIOLOGY

Proof of the virus etiology of influenza is now accepted and so is the existence of two major groups of viruses, A and B. The existence of minor antigenic variants is responsible for the description of the viruses as groups rather than types. The significance of variants is largely unknown, for no epidemiological or clinical counterparts of the particular virus strains have been identified. But the influenza viruses are singularly plastic in the laboratory, both from the standpoint of antigenic (chemical) and biological (pathogenetic) properties. It may be therefore that new antigenic strains such as have been encountered in recent years are the result of a constantly occurring evolution towards more successful pathogenic agents. Because their human hosts have not experienced such strains before, the variant viruses may spread more readily than strains derived from previous epidemics which have left behind immunological changes in the bodies of those whom they have infected.

The significance of the most recent knowledge concerning the viruses themselves, namely, the fact that the virus particles exist both as small globoid structures and as long thread-like filaments, is unknown (Chu *et al.*, 1949). Electron micrographs of the influenza viruses showing the fila-

NOTES AND PREPARATIONS

NEW PREPARATIONS

ANTISTIN CREAM AND OINTMENT, each containing 2 per cent. antistin, have been prepared for the local treatment of allergic skin disorders, either alone or in conjunction with oral antistin therapy. The ointment is stated to be suitable for dry and scaly conditions, whereas the cream with a water-miscible base is more generally preferable, especially in exposed areas. They are supplied in tubes of 20 g. (Ciba Laboratories Ltd., Horsham, Sussex.)

AUREOMYCIN (Lederle).—Supplies of this antibiotic are now available on prescription for urgent cases. Aurcomycin (Lederle) is issued in vials of 16 capsules of 250 mg. for oral use, and in vials of 25 mg. with dropper for ophthalmic use. (Lederle Laboratories Division, Cyanamid Products Ltd., Brettenham House, London, W.C.2.)

INJECTION SOLUTION B.A.L. (dimercaprol or 2,3 dimercaptopropanol), a 5 per cent. solution in arachis oil with 10 per cent. of benzyl benzoate, for intramuscular injection, is issued in ampoules of 2 ml., in boxes of 6, 12 and 100. (Allen & Hanburys Ltd., London, E.C.2.)

LACTALUMINA COMPOUND (CROOKES).—Each compound tablet contains aluminium hydroxide 2 grains, magnesium trisilicate 2 grains, magnesium oxide $\frac{1}{2}$ grain, and papain $\frac{1}{2}$ grain. The tablets have been prepared for the use of patients with dyspepsia or peptic ulcer. Supplied in cartons of 12 pocket packings, each containing 12 tablets. (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

OPTALIDON, an analgesic which is stated to relieve pain without causing drowsiness or stupor, is now again available. It is issued in tubes of 10 tablets, and bottles of 25, 100 and 250. (Sandoz Products Ltd., 134 Wigmore Street, London, W.1.)

LEAD POISONING IN BABIES DUE TO NIPPLE SHIELDS

A NOTE from the Ministry of Health draws attention to the occurrence of a number of cases of lead encephalopathy in babies resulting from the use of lead nipple shields by their mothers. Immediate administrative action is being taken to discourage the prescription and use of lead nipple shields under Part IV of the National Health Service Act, 1946, and these shields will be excluded from the list of appliances in Part I of the Third Schedule.

MEDICAL FILM

A FILM illustrating "The Technique of Sub-

cutaneous Hormone Implantation", demonstrated by G. I. Swyer, D.M., M.R.C.P., has been produced for Roussel Laboratories Ltd., by Brian Stanford, M.R.C.S., D.M.R., F.R.P.S. The film (16 mm. silent, in colour, running 7 minutes), designed for teachers of obstetrics and endocrinology for illustrating lectures, may be obtained free on application. (Roussel Laboratories Ltd., 95 Great Portland Street, London, W.1.)

PUBLICATIONS

Diets for Sick Children has been prepared by the Hospital for Sick Children, Great Ormond Street. The pamphlet deals first with the general preparation of diets, and then with diets for specific conditions. Some useful recipes are included. (The Dietitian, Hospital for Sick Children, Great Ormond Street, London, W.C.1, price 1s.)

Lewis's Diet Charts.—This set of 25 diet tables is designed for the use of physicians for handing to patients after consultation, modified to suit individual requirements. The subjects covered are: allergy, dyspepsia, peptic ulcer convalescence, ketosis, gout, obesity, heart, kidney and nervous diseases, sodium elimination, fever, gravel, chronic diarrhoea, tuberculosis, rheumatism, constipation, anaemia, and convalescence. A specimen packet of 4 copies of each chart and a twelve page booklet "Notes to Lewis's Diet Charts", price 7s.; 100 charts, assorted to suit individual requirements, price 6s.; smaller quantities 1s. per dozen, and the booklet 1s. net; plus postage. (H. K. Lewis & Co., Ltd., 136 Gower Street, London, W.C.1.)

Catalogue of an Exhibition of Books, Manuscripts and Relics, Commemorating the Bicentenary of Edward Jenner, 17 May, 1749—26 January, 1823, is published by the Oxford University Press for the Trustees of the Wellcome Historical Medical Museum. A brief biography of Edward Jenner and his work is given in the introduction, which is followed by an account of his work on small-pox inoculation. (Oxford University Press, 2s.)

Entry into Practice, published by the Medical Practitioners' Union, deals with the problems of entering general medical practice and consultant practice under the National Health Service. Some constructive suggestions are made. (Medical Practitioners' Union, 55-6 Russell Square, London, W.C.1.)

The contents of the December issue, which will contain a symposium on "Respiratory Diseases", will be found on page lxxviii at the end of the advertisement section.

origin of new outbreaks. Meanwhile, it is important to remember that the detection of a sporadic case or small outbreak of influenza does not immediately indicate a large-scale epidemic. The conditions requisite for the spread of infection are as yet imperfectly defined.

The experience of those countries which have attempted to follow their epidemics of influenza over a number of years is that a certain plan of periodicity is discernible. Influenza A is more common at two- or three-year intervals than as an annual epidemic; influenza B is experienced more rarely at four- or six-year intervals (Commission on Acute Respiratory Diseases, 1946). But in addition to the occurrence of actual epidemics, their intensity varies between a minor and major scale. In this country a large wave of influenza A used to occur every four years, but since 1939 the large waves have occurred at irregular and longer intervals, although the general biennial periodicity of influenza A has persisted. Only one largish outbreak of influenza B in Great Britain has been definitely proven since the virus was first isolated, and this occurred in 1945-46, as already mentioned.

A useful warning of the occurrence of epidemics of influenza has been obtained by following the curve of deaths from influenza in the great towns of England and Wales. Such deaths are recorded by practitioners every year, but if a sudden sharp increase occurs, it is probable that one or other of the influenza viruses is active. When the weekly deaths pass the critical figure of 100, an epidemic is in existence, and it is precisely at such times that laboratory workers detect the virus readily, either by direct recovery from specimens of throat washings or by serological methods. It would be interesting to know why the diagnosis of a death from influenza is so much more accurate in relation to the virus infection than that of uncomplicated cases, but such certainly appears to be the case.

CLINICAL FEATURES

There is little that is new to describe in regard to clinical features of influenza. The account of mild influenza in the June wave of 1918 as a short three-day fever with headache, muscular pains, shivering and cough (Ministry of Health Report, 1920) remains a fair description of that seen in recent outbreaks. Influenza is recognized not so much because of its severity but by reason of its suddenness of onset, pyrexia (although 101° F. [38.3° C.] is often the highest recorded temperature), and absence of localizing signs save those in the throat or chest. Involvement of other members of the family, milder illnesses in the young children and symptoms severe enough to necessitate bed in those of adult years, are other suggestive experiences. A mere catalogue of symptoms and signs is unhelpful in deciding upon the diagnosis in individual cases because there is no single diagnostic sign or symptom complex. In the 1937 epidemic, a dry throat with a velvety red, granular posterior pharyngeal wall was often seen, but

mentous forms resemble those of agents with a growth cycle, but it is far too early to dogmatize upon this point.

EPIDEMIOLOGY

The majority of infectious diseases exhibit a regular pattern of incidence in which infection persists endemically in the community, either in the form of sporadic cases or in the bodies of human or animal hosts which act as healthy carriers of the infectious agent. From the endemic level, epidemics arise either because of an accumulation of uninfected susceptible hosts or by circumstances favouring a spread of the infectious agent in the community. On *a priori* grounds, such a pattern would seem appropriate to influenza, for cases clinically resembling the epidemic disease occur in between actual outbreaks, although with greater frequency in winter than in summer. Yet in the sixteen years since the first recovery of influenza virus in the Hampstead laboratory (Smith, Andrewes and Laidlaw, 1933), successful identification of the virus has been almost wholly confined to periods of actual epidemicity either of localized or country-wide outbreaks.

Sporadic influenza virus infection has thus been extremely hard to prove, in spite of the work of several observers. In addition, the appearance of an epidemic in a particular country has in the past four years been less explicable on the theory of resurgence from endemic levels than on the basis of an imported infection. Such a theory as the latter has long been supported by the experience of Pickles in his country practice in Wensleydale. Yet, on a country-wide scale the B epidemic of 1945-46 was the first clear instance in which the virus seemed to creep from one area to another. It first appeared in the Pacific area and was then reported in one region after another in the United States, Central and South America, and finally, in Britain in December 1945. Since 1947, epidemics of influenza A, both in this country and in the United States, have been associated with a group of "A" strains catalogued for purely descriptive convenience as the "influenza A prime" group. Their antigenic distinctness from earlier known viruses has enabled recognition of their occurrences and mode of spread. The 1947 outbreak in this country occurred six months after the first influenza A prime outbreak, which was in Australia, and preceded that in the United States by a few weeks. The 1949 European outbreak began among the shepherds of Northern Sardinia and spread *via* Italy and France to Austria, the Netherlands, Great Britain and Iceland. It is difficult to believe that such a "winged" organism could have persisted endemically only in the Sardinian country folk, yet its initial appearance among this population remains mysterious to a degree.

The present careful study of the isolation and characters of virus strains in various countries which is being undertaken by the World Health Organization is essential, and may be the only way of reaching the answers to the general problems of survival of virus between epidemics and the

such as is now experienced from that referred to in all textbooks as "The Influenza". Those who have witnessed the sudden snatching away from a family of a young adult by the influenzal staphylococcal pneumonia described above have difficulty in believing that influenza has really turned its coat. There is every reason for believing in some other explanations, such as the more regular experience of mild influenza now than in the pre-1918 days, and the consequent partial immunization of the population which results.

The controversy regarding the nature of the 1918 pandemic is a fruitful ground for speculation, but one can only point to known circumstances such as the plasticity of the viruses, the frequent variation and possible origin of new strains with new properties. There is no reason for fearing the emergence of a new pandemic of the 1918 variety, but there is equally no reason to assume that it cannot happen again. The latter possibility remains a justification for a continued watch upon influenza epidemics and viruses and is a spur to research into means of prevention and control.

DIAGNOSIS BY LABORATORY MEANS

Two circumstances distinguish an attack of influenza from any of the many types of colds, catarrhs, pharyngitis, bronchitis or atypical pneumonias which occur sporadically all the year round. These are first, the presence of influenza virus in the throat and nose during the early stage of the illness, and secondly, the increase in amount of antibodies with specific virus-neutralizing or complement-fixing properties directed against the virus antigens, which occurs during convalescence from the disease. Tests for these specific circumstances therefore consist either in attempts to identify the virus directly by inoculation of garglings into fertile hens' eggs or ferrets, or of serological investigations. Because virus is rapidly inactivated unless frozen and stored in the cold, garglings must be sent to the laboratory within a few hours of collection, but sera can be sent by post. Blood should be collected as for the Wassermann test but two samples are required; the first should be collected within 72 hours of the onset of illness; the second ten to fourteen days later. Influenza virus tests are carried out in certain laboratories designated as Virus Reference Laboratories, such as that belonging to the Central Public Health Laboratory at Colindale, London. Positive results give little assistance to the clinician in present circumstances and tests are therefore of chief importance to those engaged in actual research upon the spread of outbreaks or in the relation of particular clinical phenomena to the virus responsible for the infection.

THE PREVENTION AND TREATMENT OF INFLUENZA

Proper treatment of the subject of the progress towards the prevention of influenza demands an historical approach and a much greater amount of space than that now available. An excellent review is given by Blake (1948). It is only here possible to outline some of the chief points which have

since then less reliance on this sign has been possible. Emphasis of congestion in the nasopharynx and posterior wall rather than upon the anterior pharynx and tonsillar region remains, however, a useful pointer and this, combined with a blocked rather than a running nose, suggests influenza rather than a streptococcal throat or cold. Similarly, influenza often blunts the tone of the voice but rarely causes the croaking, croupy laryngitis of the common febrile catarrhal respiratory disease. (An excellent account of the latter is given by the Commission on Acute Respiratory Diseases (1947)). Abdominal symptoms are relatively uncommon in influenza; diarrhoea and vomiting suggest search for intestinal pathogens rather than the influenza virus.

Pulmonary complications vary greatly in incidence. Râles or rhonchi may be elicited by repeated examination in many cases, but signs of actual consolidation occur in a minority of the total. The most common complication is probably that of a bronchitis or a bronchiolitis in which cyanosis is relatively prominent compared with the pyrexia or cough. Actual dullness and bronchial breathing indicative of pneumonia occur in two distinct groups of patients. In one, namely the postinfluenzal cases, some days or even a week or more pass after the attack of influenza and then sharp pain in the chest ushers in the pneumonia, which is usually of pneumococcal origin and follows the normal course of the latter with response to chemotherapy. Many cases are mild in severity and recover satisfactorily. More important than these are the less common, true influenzal pneumonias. These have been experienced in recent epidemics chiefly in those over forty-five and have been lethal particularly in those over sixty-five. After an ordinary beginning with symptoms of influenza, and perhaps following a temporary lull in the illness, a sudden onset of dyspnoea and cyanosis heralds a grave illness. There is but little chest pain and cough may be less prominent than the dyspnoea. The sputum may be loaded with organisms and the *Staphylococcus aureus* is often found. The course usually lasts for several days, but the rate of change of illness can be extremely rapid, even in relatively young subjects. The response to treatment even with penicillin is poor, and oxygen to relieve the cyanosis is just as important as chemotherapy. Some cases develop signs of pulmonary oedema, but in others the pulse is rapid and feeble and the blood pressure low, suggesting a peripheral vascular failure. All such cases, if fatal, fully justify notification as deaths from influenza, and laboratory work supports the belief that the influenza virus is intimately concerned in the etiology, although bacteria, and particularly the staphylococcus, play their part in determining the lung lesions.

Some authorities consider that nothing similar to the fatal pneumonias experienced in the November 1918 and March 1919 epidemics has occurred since, and it is admittedly true that the predominant involvement of the twenty to forty-five age group in the latter is seen no longer. But it is surely a question of quantity rather than quality which distinguishes the "flu"

the future may reveal the existence of variants as yet unknown and which are not contained in the vaccines now available.

Even when the vaccine has been chosen and the time of its use determined, the problem still remains of determining the character of the recipient. A widespread influenza epidemic affects children and adults alike, so that theoretically, immunization is needed on a universal scale. But many will question whether the mild influenza of recent years, which never affects more than one-fifth of the population, is really more to be dreaded than a campaign of mass immunization. Nature may have perfected a better system of immunization by mild infection than we can mimic artificially with certainty. It is obvious that one cannot ever visualize mass use of a vaccine, which is only temporary in its effects, against present-day influenza. It is even questionable if it should be used on groups such as schools or nurses or Servicemen, who normally stand in greater risk of infection than the general population. However, none will doubt that if an epidemic of the 1918 type appeared on the horizon, an effective vaccine would be greatly desired and widely used. Thus, the modern observer's viewpoint concerning the prevention of influenza is essentially that of one who is attempting to perfect a weapon for future use under hypothetical conditions. If by his experiments some benefit is conferred against a lesser evil, there will be reason for gratification, but such benefit is not the justification for the effort. If after all this any reader desires to obtain vaccine for use in special groups or on patients in whom an attack of even mild influenza might be particularly dangerous, commercial preparations are available. The vaccine, which is polyvalent for both influenza A and B, is used as a 1 ml. dose subcutaneously; being prepared from chick embryos, it must not be given to any with a history of intolerance to eggs, or of asthma or urticaria following ingestion of eggs. Only one dose is given because repetition of injection confers no further benefit.

Finally, there is nothing to write on *the treatment* of influenza which is other than a repetition of previous writers' opinions. There is no specific against influenza, nor is it certain that administration of *sulphonamides* or of *penicillin* will protect against a possible bacterial complication. In view of the special risk of influenza in the aged, however, such chemotherapy is for them worthwhile. If pneumonia or severe bronchitis ensues, the most effective form of chemotherapy, namely with penicillin, should always be practised.

References

- Blake, F. G. (1948): *Bull. N.Y. Acad. Med.*, **24**, 308.
Chu, C. M., Dawson, I. M., and Elford, W. J. (1949): *Lancet*, **i**, 602.
Commission on Acute Respiratory Diseases (1946): *Amer. J. Hyg.*, **43**, 29.
— (1947): *Medicine*, **26**, 441.
Ministry of Health Report on Pandemic of Influenza 1918-19 (1920): H.M. Stationery Office, London.
Salk, J. E. (1948): *J. Immunol.*, **58**, 369.
Smith, W., Andrewes, C. H., and Laidlaw, P. P. (1933): *Lancet*, **ii**, 66.

become apparent in the work which has been carried out on the subject of immunization with virus vaccines.

Immunization.—Unfortunately, immunity to influenza is still only imperfectly understood. Natural immunity is known to be at its peak soon after an attack of influenza and to be temporary in duration. It is also clear that age is concerned, although not in any defined way. But delineation of the basis for such naturally acquired immunity is still imperfect. Protective antibodies are clearly concerned and must constitute an important factor in defence. Yet of two individuals with the same antibody levels against the virus before an epidemic, one may be struck down and the other left. Attempts to probe the basis of a nasal factor in defence have not been very successful, although few can doubt that the nasal epithelium in some individuals is better able to protect itself than that in others. Considering the doubt which still exists as to the relative part played by antibodies and by the cells themselves in guarding the host from attack by virus, it is surprising that attempts to produce an artificial immunity should have been so fruitful and also so tempting a goal. For experimental immunization of animals susceptible to influenza, such as ferrets and mice, was an early subject of research and suggested that antibodies produced by injection of animals with killed virus vaccines afforded only a partial measure of protection against infection. Man, with previous experience of natural infection, possesses a defence mechanism which requires reinforcement rather than a primary stimulus and thus differs from the simple experimental host. Yet, even in man, it is clear that artificial immunization has serious limitations.

The first obstacle is that vaccines require time to produce an effect and exert their maximum effect in the second to the fourth week after injection. Because it is so difficult to be sure when an epidemic is to be expected and the rate of spread of infection is so rapid, the timing of immunization affords a major problem which still resists solution. It is a gamble whether immunization should be carried out in December or before or after this time; probably it is better to wait for signs of an outbreak even if there is then a risk that the vaccine will be given too late.

The second obstacle is that of determining the most suitable virus vaccine. Clearly the most potent vaccine will afford the best antibody response, yet it will also induce the biggest reactions. The latter, which are of the general character seen after T.A.B., are sufficiently unpleasant to limit the size of the individual dose of vaccine. They are apparently due to the virus rather than to impurities (Salk, 1948). Children react more fiercely than adults and require a smaller dose than is theoretically desirable in view of their less prepared defence mechanism. The reactions are less if the vaccine is given intradermally than if given subcutaneously, but it is not yet certain that this is an effective route of administration. Again, the vaccine must contain the antigen appropriate to the virus strain likely to be experienced in the forthcoming epidemic. This necessitates a polyvalent vaccine containing several strains and leaves unsettled the possibility that

abscess of the pleura, shut off from the general pleural cavity by adhesions. Distinction between these two conditions is of no little practical importance, and is rightly emphasized by thoracic surgeons as an essential factor in planning the details of operative treatment. Localization of the pus may occur peripherally, the fluid occupying the lower part of the pleural cavity behind, and varying in amount from a few ounces to several pints. Apical empyemas are much less common. Collections of pus may occur in the mediastinal region, anterior or posterior to the root of the lung, whence they may spread backwards or forwards to the chest wall. Sometimes they are found between the inferior surface of the lower lobe and the diaphragm, and occasionally in one of the interlobar fissures whence they gradually spread to the periphery.

Various pathogenic organisms may be responsible for the formation of a purulent pleural effusion, but the most common found in association with an acute empyema are the pneumococcus and the streptococcus. The former is the cause of the majority of cases of meta-pneumonic effusions; the syn-pneumonic type is mostly associated with the presence of a hæmolytic streptococcus. When empyema complicates an ordinary lobar pneumonia, the inflammatory condition in the lung has usually begun to undergo resolution, at least to some extent, before the actual formation of pus in the pleural cavity. In streptococcal cases, however, pus formation occurs in a very early stage of the disease, and streptococcal pus is often much thinner in consistence, unlike the thick creamy exudate characteristic of a pneumococcal empyema. The importance of this in relation to treatment will be discussed later.

CLINICAL AND RADIOLOGICAL FEATURES

Acute empyema.—Empyema may be acute or chronic, the latter type including tuberculous empyema, which will be considered later. The physical signs of an ordinary acute empyema may be similar to those of any other pleural effusion. On the affected side there is restriction of movement during respiration; with very large effusions there may even be some bulging of the chest wall. There is marked dullness to percussion with considerable diminution, even to absence, of the respiratory murmur, the vocal resonance, and the tactile vocal fremitus. Above the level of dullness bronchial breath sounds may be heard, and there may be a zone in this region in which ægophony is audible. The heart is displaced towards the opposite side. Radiological examination will confirm these findings and show a large area of opacity on the affected side with cardiac displacement away from it. When such a clinico-radiological picture as the above presents itself in the later stages of lobar pneumonia, especially if accompanied by a recrudescence of pyrexia after a temporary defervescence, the presumptive evidence of empyema is very strong and exploratory puncture may be expected to yield pus. The above description applies to cases in which there is a large effusion throughout the general pleural cavity. It must, however, be remembered

THE DIAGNOSIS AND TREATMENT OF EMPYEMA

BY MAURICE DAVIDSON, D.M., F.R.C.P.

Consulting Physician, Brompton Hospital.

EMPYEMA is one of the oldest known diseases, having been recognized by Hippocrates, who advocated its treatment by drainage. Although in special hospitals for chest disease, and even in general hospital practice, it is familiar enough, the number of cases actually encountered in general practice outside hospital is relatively small. Recognition of the condition at the earliest possible stage is of the greatest importance, since upon correct early treatment depends not only the immediate relief of the patient's condition, but also the prevention of those more remote effects which often result from faulty management at the outset.

PATHOGENESIS

Infection of the pleura from the outside is not a common event; it does, however, occasionally occur, as, for example, in penetrating wounds of the chest, or fracture of the ribs, especially if there has been much bleeding into the pleural cavity. More often the infection comes from within, the primary disease being in the lung itself, e.g. pneumonia, abscess and gangrene of the lung, or some other form of suppurative pneumonitis. It may spread *via* the lymphatics from a subphrenic abscess, or there may be direct spread from such conditions as mediastinal abscess or a malignant growth of the œsophagus in which breaking down of the tissues has begun to occur. Purulent pleurisy has been described as an occasional complication of various acute specific infections, such as scarlatina and influenza, but in such circumstances it probably accompanies an unsuspected pneumonia. Empyema may result from general pyæmia in which multiple abscesses form in the subpleural region and eventually rupture into the pleural cavity.

By far the most common cause is a preceding pneumonia, of which empyema is the most frequent complication, the percentage of cases, according to figures from the different London hospitals, varying from 1.2 to 7. The development of the purulent effusion may occur *pari passu* with the inflammation of the lung (syn-pneumonic empyema), or it may be a later phenomenon in the course of the disease (meta-pneumonic empyema), as is commonly the case when it complicates a typical lobar (pneumococcal) pneumonia.

It should perhaps be mentioned that empyema denotes, strictly speaking, a generalized purulent effusion of fluid within the pleural cavity. Infection of the pleura may, on the other hand, result in the formation of a localized

of a pneumococcal empyema, on which so much reliance was formerly placed, does not always present itself.

In the syn-pneumonic cases the clinical picture may be even more uncertain, and the physician may be faced with a real difficulty in deciding whether he is dealing with a solid lung or with a collection of purulent or semi-purulent fluid. As Evarts Graham (1935) has observed: "In any condition of inflammatory involvement of the lung a sudden increase in the temperature with greater prostration of the patient nearly always indicates either an extension of the pneumonic process or the beginning of an empyema. It is not always easy to make a differentiation unless the pneumonia has occurred on the contralateral side".

From what has been said it will appear that the diagnosis of an empyema is not invariably the straightforward and obvious matter that might be assumed from the comparatively simple accounts given in many standard works on general medicine or surgery. In the majority of cases of frank pneumonia, especially the pure pneumococcal infections, there is usually little difficulty, although it must be admitted that the clinical course of the disease after treatment with sulphonamides and/or penicillin is usually very different from that formerly seen when the treatment of pneumonia was mainly symptomatic and when chemotherapy and serotherapy were unknown. I have long had the clinical impression that in pneumonia treated from the outset with drugs of the sulpha group the incidence of purulent effusions is somewhat greater than was the case with those treated merely by the old-fashioned routine, but so far as I am aware there is no statistical evidence on a scale sufficiently great to warrant a dogmatic statement on this point.

One of the possible difficulties in differential diagnosis to which some reference must be made is that of distinguishing between empyema and abscess of the lung. This is more likely to arise in cases in which the collection of pus is small in quantity and limited in extent, e.g., in interlobar empyema, and in localized encysted effusions in the region of the upper lobe. Difficulty may also arise when the pus is situated between the lower lobe of the lung and the diaphragm. Interlobar effusions are usually recognizable from the appearances in skiagrams taken with the patient in the erect position. These show a wide band of opacity stretching from the mediastinum to the periphery of the chest, the shadow seen in a lateral view being particularly helpful and resembling that seen in cases of collapse of the middle lobe. Much depends upon the history and mode of onset of the illness, which may give valuable information as to the etiological factors of the case. Sudden coughing up of a large quantity of sputum, followed by the appearance in the skiagram of a fluid level, is characteristic of lung abscess. The possibility of such difficulty should always be borne in mind since, when it comes to exploratory puncture, it must be remembered that it is not advisable in case of doubt to thrust an exploring needle deeply into the chest. If during the introduction of a fine needle the operator can be

that these are not of very common occurrence and that the external evidences of empyema are by no means constant, especially when the collection of pus occupies a very limited space, in which case the physical signs and the X-ray picture are likely to be considerably modified.

The following points especially must be emphasized: First, the position of the heart may be very difficult to determine clinically, and even the X-ray picture may occasionally be misleading, since examination by a portable apparatus, on which the physician often has to rely in the event of a patient so seriously ill, does not always ensure perfect centring, and the true position of the heart may thus be uncertain. Secondly, it must be remembered that in some cases of localized empyema, especially the interlobar type, displacement of the heart may be towards the affected side: this may be a source of confusion to an observer approaching the case with the fixed expectation of finding the classical textbook picture of a pleural effusion. Moreover, it is by no means uncommon, especially in children, to find that breath sounds, often bronchial in character, are heard all over the chest, including the dull areas. I have known of more than one instance in which, because of this, the practitioner has insisted that fluid could not be present, and has maintained that the physical signs were indicative simply of pneumonic consolidation, when in reality an empyema of considerable size was present.

What has been said in regard to physical signs applies also to the X-ray appearances, which are liable to a good deal of variation, according to the size and position of the collection of pus. Quite often a basal opacity is seen with a concave upper border curving upwards and outwards from the root of the lung towards the axilla. If the empyema is encysted, the opacity may appear as a rounded shadow with a sharply defined edge which helps to distinguish it from an intra-pulmonary abscess, with which it may occasionally be confused. It is well recognized by experienced radiologists that localized collections of fluid within the chest may simulate almost any pathological condition. Diagnosis cannot necessarily be made upon X-ray evidence alone, or even upon physical signs, but must rest upon a combination of all sources of information, i.e., clinical history, physical and radiological examination, clinical pathology (blood-picture, and the like), and usually the unequivocal evidence afforded by exploratory puncture.

In the days before the advent of the sulphonamides the diagnosis of acute empyema was, perhaps, a little less difficult than it sometimes is at the present time. The typical lobar pneumonia had its well-known crisis somewhere from the seventh to the tenth day of the disease. When, after a drop in the temperature for a few days, a further rise occurred and fever then continued with no manifestation of the expected crisis, the probability of an empyema was considerable and exploratory puncture in the dull area would reveal the presence of pus. Since the routine administration of sulphonamides the well-known picture of the older textbooks has been modified to a considerable extent and the above-mentioned manifestation

Failure to ensure the observance of this principle is the chief cause of recurrence of the trouble, leading eventually to a chronic empyema. The causes of the latter have been well summarized by the late H. P. Nelson (1931-32) as follows:—

- (1) Removal of the drainage tube before the cavity is completely obliterated.
- (2) Persistence of the infection.
 - (a) Failure to remove the fibrin at the time of operation.
 - (b) Drainage opening not at the bottom of the cavity.
 - (c) Drainage tube too long.
- (3) Delayed expansion of the lung.
 - (a) Thick visceral pleura due to (2).
 - (b) Broncho-pleural fistula.
 - (c) Fibrosis of the lung.
- (4) Foreign body.
- (5) Tuberculosis, actinomycosis, or growth.

Choice of the appropriate moment to perform an open operation is obviously a matter of good surgical judgment, and implies a proper compromise between two extremes. Premature operation, in a stage when the underlying pneumonitis is still in progress, is responsible, as the Empyema Commission showed, for a preventable increase in mortality. On the other



FIG. 1—Skiagram (diagrammatic) from a case of empyema after operation. This postero-anterior view shows a large cavity and sinus filled with opaque oil.

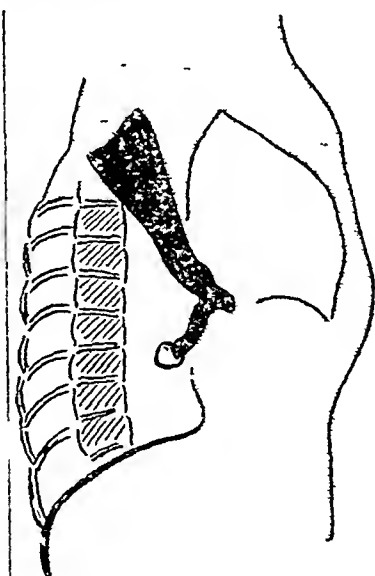


FIG. 2—Skiagram (diagrammatic) from the same case as fig. 1. This lateral view shows the bend in the track of the sinus preventing the passage of a probe into the cavity.

hand, undue delay may be a cause of failure to obliterate the empyema cavity, and may result in a chronic empyema with all the disadvantages and secondary risks which this condition is likely to entail. In open operation it is important first to re-

move as much of the fibrin and clots as possible at the outset, and secondly, to promote sterilization and obliteration of the cavity by gentle irrigation with Dakin's solution and by avoidance of premature removal of the drainage

certain of pleural thickening by reason of the sense of resistance to the needle, he can then proceed with safety. Otherwise, if he is dealing with an intra-pulmonary abscess in the early stages, with a free pleura, there is danger of infecting the pleural cavity, hitherto unaffected, and so creating an empyema in addition to the lung abscess, an accident which would add considerably to the gravity of the condition, possibly with fatal consequences.

In very severe infections a purulent effusion may be found in both pleural cavities. Bilateral empyema is not a common phenomenon; I mention it here as one of the possible sources of error in diagnosis, avoidance of which can usually be ensured by a lively remembrance of its existence.

TREATMENT OF ACUTE EMPYEMA

Treatment of an empyema should not merely achieve the immediate object, i.e., the removal of the pus by drainage and the saving of the patient from death by toxæmia, but should also ensure adequate re-expansion of the collapsed lung with ultimate obliteration of the empyema cavity. Drainage is ordinarily effected by rib-resection with the creation of an open pneumothorax. Choice of the appropriate moment for rib-resection is one of the most important points in the modern treatment of this condition. Since the publication of the report of the American Empyema Commission (1918) thoracic surgeons have recognized the imperative necessity, especially in streptococcal cases, of avoiding drainage by open operation in the earlier stages when active inflammation of the underlying lung is still in progress, when the effusion has not yet become limited in extent by fibrinous adhesions, and when the mediastinum is still mobile. In these circumstances it is essential to postpone the radical drainage operation, although considerable benefit to the patient may be achieved by removal of the pus by successive aspirations or, still better, by the method of closed intercostal drainage, which should certainly be instituted as soon as it is evident that a large quantity of infected fluid is present. This comparatively simple operation can be carried out with the patient in his bed and with local anæsthesia, radical drainage being deferred until later, when the mediastinum has become relatively fixed by adhesions and the patient's vital capacity has been somewhat raised. I have emphasized this especially in regard to acute streptococcal empyema, but the same principle applies in some cases of pneumococcal or other infections, especially in debilitated children whose vital capacity and general resistance have been much lowered. The shock to a very young child may be considerable and the risk much greater than to an adult in similar circumstances. No hard and fast rule can be laid down as to when preliminary aspiration should precede the standard drainage operation; the question must be one for the judgment of the surgeon in charge.

The other point of supreme importance in treatment is the maintenance of adequate drainage after rib-resection and its continuance until it is certain that the resulting sinus is closing from below and that removal of the drainage tube will not result in the persistence of residual pockets.

any decision to undertake further extensive exploratory or plastic operations.

TUBERCULOUS EMPYEMA

The development of a pyothorax in long-standing pulmonary tuberculosis is a phenomenon well known to the chest specialist, of whose practice it constitutes one of the bugbears. The condition may arise during the natural course of the disease in a patient who has undergone purely routine treatment. In most cases, however, it occurs as a sequel of pleural effusion arising during a period of artificial pneumothorax therapy. The occurrence of a fluid onset in such circumstances is always a matter of some anxiety to the physician. In not a few cases the effusion clears up and eventually the pneumothorax cavity becomes obliterated. In other cases the fluid persists in spite of periodic aspiration with gas-replacement. If degenerated leucocytes are discovered in the fluid, which may also be found to contain tubercle bacilli, the condition may be said to constitute a tuberculous empyema in the earliest stage, even though the fluid, although perhaps turbid, cannot be described as actual pus in the ordinary sense of the word.

It has been suggested by some, in view of the generally unfavourable prognosis in regard to tuberculous empyema, that thoracoplasty should be undertaken at this stage. Whilst appreciating the radical principles underlying this view I cannot help feeling that it is hardly justifiable to advocate it as a routine. Not a few cases of this sort will yield to periodical pleural lavage, and it seems to me reasonable to give this a preliminary trial, especially since the introduction of the modern antibiotics, such as streptomycin, and *para*-aminosalicylic acid. Secondary infection with pyogenic organisms increases the difficulty of treatment and renders the formation of a chronic sinus almost inevitable. The decision to undertake plastic operations is a responsible one and involves much consideration of individual circumstances, with due attention to the principle that should underlie the treatment of all tuberculous lesions, i.e., the recollection that tuberculosis is a systemic infection, and the necessity of treating the patient as well as the disease. Plastic surgery may involve a much longer period than is required for the surgical treatment of lung disease uncomplicated by extensive pleural involvement, and thoracoplasty may have to be performed in three or four, or even more stages. The ultimate objective is, of course, to bring the visceral and parietal layers into as close an apposition as possible if final cure is to be achieved.

References

- American Empyema Commission (1918): *J. Amer. med. Ass.*, 71, 366, 443.
 Davidson, M. (1948a): "A Practical Manual of Diseases of the Chest", 3rd edition, Oxford, p. 505.
 — (1948b): *Post-grad. med. J.*, 24, 57. (Case 1).
 Graham, E. A., Singer, J. J., and Ballon, H. C. (1935): "Surgical Diseases of the Chest", London, p. 127.
 Nelson, H. P. (1931-32): *St. Barts. Hosp. J.*, 39, 170.

tube. Re-expansion of the lung is encouraged by suction drainage, reinforced later by suitable breathing exercises controlled by expert physiotherapists. Irrigation of the cavity is carried out either by insertion of two rubber tubes or by the use of a 'Tudor Edwards' flanged tube specially designed for the purpose. The final decision to remove the drainage tube is almost always a matter of some little difficulty. It is a wise and safe rule, before removing the tube entirely, to insist upon a pleurogram (X-ray of the sinus after introduction of iodized oil, fig. 1 and 2). By this it is often possible to show the presence of a cavity or of an extension of the main sinus, which, because of a kink in the latter, could not be demonstrated by the passage of a probe (Davidson, 1948a).

During the later stages of treatment, in addition to specific physiotherapy to encourage re-expansion of the lung, special attention should be paid to the patient's nutrition, and care should be taken to ensure the provision of an adequate and well-balanced diet (up to 3,500 calories daily), with suitable tonics and any other symptomatic treatment that circumstances may indicate.

CHRONIC EMPYEMA

Chronic empyema may appear as a collection of pus in the pleural cavity which has persisted for a long period, the original condition having passed unrecognized; or it may be found as a sequel to acute empyema in which treatment has failed to close the cavity, so that the patient is left with a persistent sinus, which may or may not undergo periodic temporary healing. Sufficient has already been said to indicate that, in a large proportion of cases at least, the occurrence of a chronic empyema is a result of inadequate treatment at the outset of the acute condition which preceded it; in other words, of inadequate drainage. Apart from the obvious inconvenience of a persistent discharging sinus, the patient with a chronic empyema is always subject to the potential risk of a metastatic cerebral abscess (Davidson, 1948b), to say nothing of the chronic toxæmia and general ill-health which often characterize this condition. Toxic myocarditis and renal damage are not infrequent concomitants.

Treatment must be planned with regard to the circumstances of the individual patient and with due avoidance of precipitancy in surgical intervention. Accurate estimation of the dimensions and limits of the sinus by pleurograms is an essential preliminary. Not a few cases may be dealt with by the re-establishment of adequate drainage and by continued pleural lavage with Dakin's solution, without having recourse to extensive operative manipulation, including decortication. If these measures prove insufficient and further operative intervention is necessary, it must be realized that treatment may, and probably will, extend over a long period, and that considerable harm may result from injudicious attempts to do too much at a time. Careful routine investigation of the patient's general condition, with special attention to the cardiovascular and renal systems, should precede

the lung. The aim should be to describe the types of pneumonia according to their causes rather than in terms of the varying clinical picture.

ETIOLOGY

The evidence that primary atypical pneumonia is a virus disease is largely circumstantial. The similarity of the cases in different outbreaks suggests a common or similar cause and the few fatal cases have shown a distinctive pathology. Viruses are known to be capable of causing pneumonia in small laboratory animals.

When human cases have been searched for a virus the evidence has often been hard to find, possibly because of the inherent difficulties in the technique of virus studies. From the filtered and bacteriologically sterile sputum of cases of atypical pneumonia a virus has been transmitted to chick embryos (Eaton *et al.*, 1944) and later shown to cause pneumonia in cotton-rats. The virus was neutralized by the serum of patients convalescent from primary atypical pneumonia. It was thought to account for 60 per cent. of cases of atypical pneumonia. Mouse inoculation and the demonstration of specific antibody in the patient's serum have shown that in a few, usually serious, cases of atypical pneumonia the psittacosis virus may be responsible, as also may be the virus of lymphocytic choriomeningitis.

Clinical similarity does not therefore mean a similar etiology, and some apparently characteristic cases of primary atypical pneumonia may have a non-viral cause. This was well shown by an outbreak of atypical pneumonia which was later found by serological tests (Caughey and Dudgeon, 1947) to have been caused by the *Rickettsia burneti* of "Q" fever. One outbreak followed the termination of an epidemic of infective hepatitis, and certain features of it, such as anorexia and liver enlargement without icterus, suggested that the viruses of the two diseases might be related. This is supported by the fact that the spleen is sometimes enlarged in atypical pneumonia, and by the rare combination of atypical pneumonia with apparent acute hepatitis.

Lastly, there is some evidence provided by experiments on human volunteers. The United States Commission on Acute Respiratory Diseases (1945) found that a respiratory illness like that of primary atypical pneumonia developed in 3 out of 12 volunteers who received intranasal inoculations of pooled sputum from cases of primary atypical pneumonia, whereas 18 cases receiving autoclaved material did not develop symptoms.

EPIDEMIOLOGY

Although an increased incidence can be expected in the winter months the disease may occur at any time of the year. It may even assume epidemic proportions in the summer, as happened in 1946 in Hungary when 75,000 cases are estimated to have occurred.

PRIMARY ATYPICAL PNEUMONIA

By C. ALLAN BIRCH, M.D., F.R.C.P.

Physician, Chase Farm Hospital, Enfield.

MANY cases of pneumonia do not conform to the classical description of an acute illness beginning with a rigor and showing a quick, bounding pulse, hot dry skin and clear evidence of chest mischief, such as rapid, shallow breathing, pleural pain, viscid rusty sputum and the dull noisy lung of consolidation. The label "pneumonia" covers much, and its too easy application accounts for the stories of doctors who never lose a case, and thereby gain great credit in the eyes of the relatives.

What may be regarded as "typical" pneumonia is caused, as a rule, by a pneumococcus. When a streptococcus, staphylococcus or other unusual organism is responsible, the disease and its sequels may vary considerably. Even pneumococcal pneumonia may be atypical in many ways. If a main bronchus is blocked the signs may resemble those of fluid. The clinical picture may be greatly modified by age, habits and mental state, and by exaggerated referred symptoms such as abdominal pain and meningism. In severe mental disease the patient may remain euphoric throughout his illness. Grave toxæmia may so poison the higher centres that the patient will similarly remain undistressed, as exemplified by the old saying "beware of a pneumonia which smiles at you". All these variations, however, are examples of the different effects of the same seed in different soils. In primary atypical pneumonia the seed is different.

Older clinicians will recall cases of pneumonia and small outbreaks which differed greatly from the classical type. In recent years these atypical cases have become much more common, and since the beginning of the last war about 300 papers have appeared on the subject of atypical pneumonia. Attention was focused on these cases because of their failure to respond to sulphonamide drugs, which differentiated them from the pneumonias caused by specific bacteria.

TERMINOLOGY

There is good evidence that atypical pneumonia of the type under consideration is a virus disease, but as more than one virus may cause it the American term "primary atypical pneumonia" is probably the best in the present state of knowledge. Even this label has caused misgivings because it has suggested to some that all these cases have a common cause, and also because of the great variations in the manifestations of "typical" (pneumococcal) pneumonia itself. The term "pneumonitis" sometimes used for these cases is a bad one and should be discarded, since it really means no more than does the older term "pneumonia"—namely, inflammation of

different outbreaks, some being much milder than others. This is a clinical point suggesting that more than one virus may be responsible.

RADIOLOGICAL FINDINGS

These can be demonstrated in the early stages and before definite clinical signs appear. The sequence is an increase in size of the hilar shadows followed by infiltration spreading outwards, and showing as a fine haziness with patches of increased density, particularly in the lower lobes. The distribution of lesions follows the bronchi and need not be strictly lobar as in "ordinary" pneumonia. Lesions are bilateral in about one-fifth of the cases. The shadows are not so dense as in bacterial pneumonia and may show a reticular appearance. This is what would be expected from the (admittedly scanty) histological evidence, which shows an interstitial pneumonia with only a thin deposit of exudate on the alveolar walls. Sometimes a miliary appearance results ("disseminated focal pneumonia").

In milder ambulatory cases small patches resembling early tuberculous lesions may be found. Similar transient opacities have been found in the common cold (Kennedy, 1943). It must not be assumed, however, that all shadows in the lungs in cases of upper respiratory catarrh are caused by primary atypical pneumonia. They may be small patches of "aspiration pneumonia" or, as Scadding (1948) terms it, "infected atelectasis".

LABORATORY FINDINGS

The white cell and differential counts are often within normal limits, but in some outbreaks counts slightly higher than normal have been found. As similar counts can be found in bacterial pneumonia great stress cannot be put on the white count in diagnosis. The sputum shows a mixed growth of organisms none of which is definitely pathogenic. The presence in the serum of agglutinins which react at refrigerator temperature to human group O red cells has been noted in up to 80 per cent. of cases. The level of the titre depends upon the severity of the disease and is diagnostic if it was negative during the acute phase and then became positive to a titre of 1 in 8 to 1 in 16. The test is not specific for any one virus.

DIAGNOSIS

A positive diagnosis is not easy in the early stages and, except in an epidemic, is generally reached by exclusion. An early chest X-ray examination may be suggestive. In the absence of this, the failure to respond to sulphonamides or penicillin should arouse suspicion. In view of the possibilities of treatment by the newer antibiotics early diagnosis should be sought by careful assessment of the clinical, radiological and pathological findings.

The *incubation period* seems to be about ten to fifteen days. Case-to-case infection is slight. In some outbreaks nurses and doctors attending patients have been especially susceptible. The period of infectiousness is not known, and as non-pneumonic forms of the disease, i.e. upper respiratory infections, are probably not uncommon it does not seem necessary to nurse cases in strict isolation.

Epidemics in the newborn, with a mortality rate of 20 per cent., have been described by Adams (1948). The mothers had signs of upper respiratory infection before delivery. The babies showed sneezing, coughing, dyspnoea and cyanosis, and a moderate pyrexia. In pharyngeal smears epithelial cells were found to contain cytoplasmic inclusion bodies such as occur in other known virus diseases.

CLINICAL FEATURES

The essential features of primary atypical pneumonia can be summarized as follows:—

- (1) The onset is insidious with generalized symptoms.
- (2) Young adults are chiefly affected.
- (3) Physical signs are scanty and less striking than the X-ray findings.
- (4) The sputum is mucoid or muco-purulent but not rusty, and contains a variety of organisms.
- (5) The leucocyte and differential counts are normal.
- (6) Cold agglutinins may be found in the serum.
- (7) The disease does not respond to sulphonamides or penicillin.
- (8) The course is relatively benign, although often prolonged, and complications are rare.

In most cases the onset is insidious, with fever, headache and chills. It is certainly less abrupt than influenza. There may be a prodromal cold. A dry cough is usual and, later, muco-purulent sputum appears in which a variety of organisms may be found. The pulse and respiratory rates are often within normal limits, and the rapid shallow breathing of classical pneumonia does not occur. The temperature rise is usually much lower than in bacterial pneumonia, the average peak being a little over 100° F. (37.8° C.). Chest examination shows scanty signs, such as a few râles, in surprising contrast to what X-rays may reveal.

In mild cases the temperature is normal within ten days, and if no skiagram is taken it may be impossible to say whether the patient has had pneumonia or not. Many of these cases were probably labelled "feverish chill" in former days. The picture of primary atypical pneumonia may, in fact, vary from a mild upper respiratory catarrh with transient radiological signs, to a severe illness with lung consolidation lasting for several weeks. Most cases have run a mild, if prolonged, course. A few have shown alarming, although non-fatal, complications, such as meningo-encephalitis.

The clinical picture and also the laboratory findings have varied in

They found that whereas half the penicillin cases recovered fairly rapidly, in all those treated with aureomycin recovery was prompt and invariable.

Aureomycin hydrochloride (Lederle) is dispensed in capsules of 250 mg. The dose is 1 g. by mouth every six hours until the temperature is normal, and then every eight hours for two or three days. The drug is now available in England, on prescription, for urgent cases.

Chloromycetin.—Wood (1949) reported a case of primary atypical pneumonia in a man of forty-two. All the diagnostic criteria were fulfilled, and penicillin and sulphadiazine were without effect. Sudden improvement began within twelve hours of giving chloromycetin, with subsequent complete cure. The drug is supplied by Parke Davis and Co. in capsules containing 250 mg. The dose is 0.5 g. by mouth every two or three hours until 3 g. have been taken, and then 0.5 g. four times a day. Because of the persistent, intensely bitter taste, it is best to give the capsules just before a bland liquid feed which will leave the stomach quickly.

CONCLUSION

In conclusion, a word must be said in deprecation of a recent tendency to assume that because potent sulphonamide drugs and antibiotics are available, treatment is now simply a matter of "giving these". Patients can still recover from serious illness for which the newer remedies are not specific. Even if the new antibiotics come up to expectations, the skilful use of measures to relieve symptoms and to conserve the patient's strength will still be important in primary atypical pneumonia as in all illnesses, for it will always be the patient and not his disease which is the entity. Trousseau's famous remark "*Il n'y a pas des maladies; il n'y a que des malades*" still holds.

References

- Adams, T. M. (1948): *Amer. J. Dis. Child.*, 75, 544.
Caughey, J. E., and Dudgeon, J. A. (1947): *Brit. med. J.*, ii, 684.
Eaton, M. D., Meiklejohn, G., and van Herick, W. (1944): *J. exp. Med.*, 79, 649.
Finland, M., Collins, H. S., and Wells, E. B. (1949): *New Eng. J. Med.*, 240, 241.
Kennedy, T. A. (1943): *Lancet*, i, 769.
Kneeland, T., Jun., Rose, H. M., and Gibson, C. D. (1949): *Amer. J. Med.*, 6, 41.
Meiklejohn, G., and Skragg, R. L. (1949): *J. Amer. med. Ass.*, 140, 391.
Reich, N. E., Ciacolo, L. F., and Reinhart, J. B. (1947): *Amer. Pract.*, 11, 85.
Scadding, J. G. (1948): *Lancet*, i, 89.
Schoenbach, E. B., and Bryer, M. S. (1949): *J. Amer. med. Ass.*, 139, 275.
U.S. Commission on Acute Respiratory Diseases (1945): *Ibid.*, 127, 146.
Wood, E. J. (1949): *Lancet*, ii, 55.

TREATMENT

At the time of writing, the treatment of these cases is to give a sulphonamide, say, sulphadimidine (sulphamezathine), up to 10 g. a day, or penicillin, 500,000 units a day, as soon as lung involvement is suspected. When failure to influence the disease is apparent after seventy-two hours or so, and laboratory and X-ray evidence support the diagnosis, it would be reasonable to give chloromycetin, which is now available in England (see p. 501). Initial failure of sulphonamides and penicillin, however, does not mean that they have no further place in treatment. When the illness is prolonged, secondary invasion by pyogenic organisms is shown by the sputum findings, a sharp rise in the white cell count, and increased density in the shadows shown on the X-ray film, may call for specific therapy. The sensitivity of the organisms, to whichever drug it is proposed to use, should first be demonstrated.

Symptomatic treatment is important for the patient's comfort. The cough is often troublesome and has been severe enough to crack ribs. Adequate doses of codeine are needed. Hypnotics should not be withheld and the practitioner should use the one he knows best. Morphine may be given, particularly if there is much pain. Otherwise, insomnia is well managed by an evening dose of a quick-acting drug such as butobarbitone (soneryl) 3 grains (0.2 g.), together with a delayed acting tablet to avoid early waking (seconal, 3 grains [0.2 g.] in "enseal" form).

Attempts at specific treatment have been made by giving whole blood transfusions from convalescent patients (Reich *et al.*, 1947). In infants, concentrated human gamma globulin is recommended. The dose is 0.1 ml. per lb. (0.22 ml. per kg.) body weight, by intramuscular injection.

The illness takes more out of the patient than might be imagined from the not very stormy fever. A period of convalescence is therefore advisable. Some physicians use the sedimentation rate to determine its length, but too rigid adherence to this test alone may call for an unduly long absence from work.

Newer antibiotics in treatment

Encouraging reports are available on the use of aureomycin and chloromycetin in primary atypical pneumonia.

Aureomycin.—In three recent articles (Finland *et al.*, 1949; Schoenbach *et al.*, 1949; Kneeland *et al.*, 1949) a total of 43 cases treated with aureomycin are reported in detail: 42 showed clinical improvement within three days of taking the drug and the temperature was usually normal within forty-eight hours of starting treatment. Although there were no controls the uniformity of response points to the effectiveness of aureomycin. The only control series published to date is that of Meiklejohn and Skragg (1949), who treated 22 patients with aureomycin and gave penicillin to 20 others. Strict criteria for a diagnosis of primary atypical pneumonia were used.

They found that whereas half the penicillin cases recovered fairly rapidly, in all those treated with aureomycin recovery was prompt and invariable.

Aureomycin hydrochloride (Lederle) is dispensed in capsules of 250 mg. The dose is 1 g. by mouth every six hours until the temperature is normal, and then every eight hours for two or three days. The drug is now available in England, on prescription, for urgent cases.

Chloromycetin.—Wood (1949) reported a case of primary atypical pneumonia in a man of forty-two. All the diagnostic criteria were fulfilled, and penicillin and sulphadiazine were without effect. Sudden improvement began within twelve hours of giving chloromycetin, with subsequent complete cure. The drug is supplied by Parke Davis and Co. in capsules containing 250 mg. The dose is 0.5 g. by mouth every two or three hours until 3 g. have been taken, and then 0.5 g. four times a day. Because of the persistent, intensely bitter taste, it is best to give the capsules just before a bland liquid feed which will leave the stomach quickly.

CONCLUSION

In conclusion, a word must be said in deprecation of a recent tendency to assume that because potent sulphonamide drugs and antibiotics are available, treatment is now simply a matter of "giving these". Patients can still recover from serious illness for which the newer remedies are not specific. Even if the new antibiotics come up to expectations, the skilful use of measures to relieve symptoms and to conserve the patient's strength will still be important in primary atypical pneumonia as in all illnesses, for it will always be the patient and not his disease which is the entity. Trousseau's famous remark "*Il n'y a pas des maladies; il n'y a que des malades*" still holds.

References

- Adams, T. M. (1948): *Amer. J. Dis. Child.*, 75, 544.
Caughey, J. E., and Dudgeon, J. A. (1947): *Brit. med. J.*, ii, 684.
Eaton, M. D., Meiklejohn, G., and van Herick, W. (1944): *J. exp. Med.*, 79, 649.
Finland, M., Collins, H. S., and Wells, E. B. (1949): *New Eng. J. Med.*, 240, 241.
Kennedy, T. A. (1943): *Lancet*, i, 769.
Kneeland, T., Jun., Rose, H. M., and Gibson, C. D. (1949): *Amer. J. Med.*, 6, 41.
Meiklejohn, G., and Skragg, R. L. (1949): *J. Amer. med. Ass.*, 140, 391.
Reich, N. E., Ciacolo, L. F., and Reinhart, J. B. (1947): *Amer. Pract.*, 11, 85.
Scadding, J. G. (1948): *Lancet*, i, 89.
Schoenbach, E. B., and Bryer, M. S. (1949): *J. Amer. med. Ass.*, 139, 275.
U.S. Commission on Acute Respiratory Diseases (1945): *Ibid.*, 127, 146.
Wood, E. J. (1949): *Lancet*, ii, 55.

ACUTE RESPIRATORY INFECTIONS IN INFANTS

By R. E. BONHAM-CARTER, M.B., M.R.C.P.

Physician, the Hospital for Sick Children, Great Ormond Street; Assistant Physician, University College Hospital.

THE importance of these infections in infants from birth to two years of age lies in the fact that the Registrar-General's reports, and the reports of the Chief Medical Officer of Health, show an increasing mortality rate in these infections with decreasing age. Nor is this the whole story, for in the study of chronic lung disease, Field (1949) and many others have shown how often there is a history of respiratory infection under the age of two, and although cause and effect cannot be directly shown here, this finding recurs so constantly that it appears significant.

The division of respiratory infections into upper and lower, meaning the pharynx and larynx upon the one hand, and the trachea, bronchi, bronchioles, lung parenchyma and pleura on the other, although arbitrary, serves a useful clinical purpose. It is arbitrary because in most of these infections both upper and lower respiratory tracts are involved.

UPPER RESPIRATORY INFECTIONS

The coryzas.—In infants, the common cold has to be taken more seriously than in later life, for although it is not a frequent cause of illness in newborn babies, yet epidemics of diarrhoea and vomiting in nurseries have been traced to colds among mothers or staff. And in this group, too, they are more often followed by pneumonia than at any other time, except old age.

The fact that in neonates and infants coryza does not always present with sneezing, running nose and cough, but instead often misleads the clinician by presenting with a refusal of food, loss of weight, pyrexia, or alarming diarrhoea and vomiting, makes recognition of the symptoms important. The diagnosis can only be made by inspection of the nose and throat, where a fiery red mucous membrane, sometimes with pus follicles upon the tonsils and occasionally with a postnasal drip of muco-pus, will be seen. During this inspection it must be remembered that a yelling baby has a very red pharyngeal mucosa. Postnasal and throat swabs usually grow mixed organisms, but in neonates, *Staphylococcus aureus* will often be found.

In the newborn, weakly babies, or premature infants, these infections must be taken seriously and treated promptly, and it is worth while giving penicillin and sulphonamides in full doses (see p. 508) to prevent complications. In older babies, little can be done except symptomatic treatment. Keeping the child indoors and, if necessary because of pyrexia, in bed. In

both groups, segregation from other children of the same age is desirable. In obstetric hospitals these babies should be isolated, preferably with their mothers. Day nursery children should not be allowed to attend and so infect the whole nursery.

Diarrhœa and vomiting is the most dangerous complication of these common infections. When it happens, correction of the fluid loss by mouth, subcutaneously or intravenously, must be undertaken at once and the loss of salts also promptly corrected. A solution of half-strength normal saline with 5 per cent. glucose added is simple to obtain, and may be given by mouth in these cases. Breast-fed babies should not be taken off the breast, but if there is difficulty in sucking, the nose may be kept clear with a solution of ephedrine, $\frac{1}{2}$ per cent., and sulphacetamide, 10 per cent., in saline, two or three drops in each nostril before each feed, and when the nose is blocked.

The ease with which young infants get *otitis media* makes it necessary to examine the ear drums regularly, at least daily. Although otitis media may be insidious in onset, it should always be suspected in any child with recurrent bouts of screaming or crying, whether or not there is an upper respiratory infection. In infants, it is better to do a diagnostic myringotomy when a doubtful drum is seen, than to wait for the drum to bulge. After the myringotomy has been done, care must be taken that the wound is not closed again in a few hours by sticky secretions. This is particularly likely to happen in dehydrated infants. The myringotomy may be kept open by gentle syringing with saline from a soft rubber rat-tailed syringe, and may be necessary as often as two-hourly.

Tonsillitis.—Infection of the lymphatic tissue of the nasopharynx is a common cause of illness in infancy; although more common over the age of six months, and particularly so in London, it can occur anywhere at any age. The inflamed mucous membrane and pus follicles, or even a purulent membrane, may be seen on inspecting the throat. The treatment is the same as for the coryzas and their complications, but more attention can be paid to the results of throat swabs, which should be taken to exclude diphtheria in all cases when a membrane is seen. Here again, a careful watch must be kept upon the ears, for otitis media is even more likely when tonsillitis is present.

LOWER RESPIRATORY INFECTIONS

Bronchitis.—The presence of palpable or audible rhonchi all over the chest, when these are sonorous and give the impression of mucus flapping about in large bronchi, justifies the diagnosis of bronchitis, but care must be taken in case these loud noises overlie and make inaudible the fine rhonchi of bronchiolitis, the crepitations of pneumonia, or the signs of collapse, for it is only when these are present that a serious view need be taken.

Little can be done for the treatment of bronchitis in infants, except prevention of the spread of infection to the smaller bronchi and lung tissue. The difficulty of giving liquefying expectorants makes the dictum that they

are useless save in emetic doses true in this age-group. Certainly a vomit results in coughing, which clears the chest. Postural drainage in infants is difficult to maintain, and it is dangerous to nurse a sick infant on his face tipped over a pillow, for he may suffocate. Nurse the child on his back with the end of the cot raised a foot or so and with his feet tied by a loose flannel bandage to the cot to prevent sliding up the bed. This position will not drain the upper lobe or posterior bronchi, but if the child's position is frequently changed and he is sat up for feeding and so on, it is adequate. Steam is probably the best method of liquefying bronchial secretions, and a kettle placed at a safe distance, at least three feet from the baby, allowing its steam to circulate under a tent of blankets, is the method of choice. Compound tincture of benzoin, 60 minims (3.5 ml.) to one pint of water, may be added to the kettle.

Bronchiolitis.—The extension of the inflammatory process into the smaller bronchioles is serious. It is the forerunner of lobular collapse of lung and subsequent infection and broncho-pneumonia. Its treatment does not differ except that sulphonamides and penicillin should be given at once (see p. 508). Cyanosis may be treated with oxygen in a tent or box or, if these are not available, by bilateral nasal catheter. It is often difficult to determine whether oxygen for cyanosis or steam to liquefy secretions is the proper treatment. The rule here is that if oxygen relieves the cyanosis it is correct; if it does not it should be assumed that it is not reaching the alveoli, and bronchoscopic aspiration must be tried. Little is to be gained by the use of atropine or other drugs used in an attempt to reduce bronchial secretion, for these render the secretion more viscid and more likely to block the bronchi.

Acute laryngotracheo-bronchitis.—This dangerous disease is sometimes known in America as "acute epidemic epiglottitis". It is more common in America and Canada than here, but is worth mentioning because it is not generally recognized, probably because of its relative rarity. It attacks principally children under the age of two years and only 5 per cent. of cases occur over the age of six. Boys are affected nearly twice as often as girls. The untreated mortality rate is 80 per cent. The onset is sudden and the course rapid. An infant with a croupy cough, with or without coryza, develops increasing respiratory obstruction with stridor, at first inspiratory, and later both inspiratory and expiratory. There are bronchitic signs all over the chest and sometimes patches of collapse. Cyanosis, sometimes of the "heliotrope" colour described in the 1918 epidemic of influenza, develops quickly and asphyxial death occurs in twenty-four to seventy-two hours if nothing is done. Morgan and Wishart (1947), in a review of 549 cases in Canada, recommend early tracheotomy for spasmodic croup, with frequent bronchoscopic drainage. This treatment, they say, has lowered the mortality from 80 to 35 per cent. Penicillin and sulphonamides should be used, but as these authors base their belief in the virus etiology of the disease partly upon the inefficacy of these drugs, they can only be used with

the object of preventing secondary infection. After bronchoscopic drainage, oxygen can be used to relieve cyanosis. Post-mortem material shows an inflammation of the whole respiratory tract from the pharynx to the smallest bronchiole, involving the cords, and sometimes so intense as to cause massive sloughing. Moncrieff and Weller (1949) suggest using chloromycetin, 0.25 g. four-hourly, for this condition.

PNEUMONIA

Scadding's (1946) classification of the pneumonias is applicable to this age-group, although it is difficult in the neonatal period to distinguish between acute specific pneumonia occurring with a neonatal septicæmia and an inhalation pneumonia.

(1) *Acute Specific Pneumonias*

Staphylococcal pneumonia.—In the neonatal period the organism causing pneumonia in more than 90 per cent. of cases is the *Staphylococcus aureus*, and partly because of this high figure it remains a principal cause of infections of the respiratory tract under the age of two years. In the newborn, pneumonia, which may be either lobular or lobar in distribution, is the result of neonatal sepsis giving rise to a staphylococcal septicæmia. The occurrence of this condition in infants' wards or nurseries must be regarded as a failure in the technique of nursing the newborn.

Treatment must be prompt, and should be started as soon as any signs are observed in the chest. No delay pending exact diagnosis or radiological examination can be allowed. The dosage of *penicillin* and *sulphonamides* should be at the highest level, and every device to isolate the organism and find its sensitivity to sulphonamides and the antibiotics must be tried, for so many of these staphylococci are resistant. If the organism is isolated in a nursery or ward it must be tracked down to its origin and eliminated. The baby should be isolated, preferably with the mother, and nursed with the precautions usual in infectious illness. Postnasal swabs and repeated blood cultures may be necessary to obtain the infecting organism. When an organism resistant to sulphonamide and penicillin is found, *streptomycin* in doses of 0.02 g. per lb. (0.044 g. per kg.) body weight per day, divided into aliquot doses and given intramuscularly at six-hourly intervals, may be used for a maximum period of four days, by which time the organism will have been knocked out, or have become resistant to streptomycin also. Aureomycin and the new antibiotics have yet to be tried in these infections, but they hold out good hope of success and are much less toxic than streptomycin.

Empyema and lung abscess are common complications. Air-containing, cyst-like cavities also develop, which can be seen to regress slowly with treatment.

Pneumococcal pneumonia.—Before the advent of the sulphonamides and penicillin the difference in prognosis in childhood between lobar and lobular pneumonia was marked. The mortality of lobar pneumonia, although it varied inversely with age, and also varied in different series of

cases, was somewhere between 10 and 30 per cent. The mortality of broncho-pneumonia was always higher, but in the under-two age-group this difference was not so marked. With penicillin and sulphonamides both mortality rates have been greatly reduced, that of lobar pneumonia now being around 5 per cent. Therefore penicillin and sulphonamides should both be given in full doses to children with lobar pneumonia. An oxygen tent (or box) for cyanosis, and brandy in doses of 5 to 10 minims (0.3 to 0.6 ml.) for circulatory failure, constitute the treatment. Penicillin and sulphonamides should be given until the temperature, respiration rate and pulse have been normal for three days; usually they fall dramatically within the first forty-eight hours.

As Chaplin (1947) has shown, the complication of *empyema* in infants due to pneumococci and streptococci has become much less frequent since the introduction of penicillin and sulphonamides, but hardly any reduction has occurred in the incidence of staphylococcal empyema.

The frequency with which *otitis media* complicates pneumonia in infants makes regular inspection of the drums a necessity. It is a frequent cause of sustained temperature after forty-eight hours of treatment.

(2) *Aspiration Pneumonias*

Inhalation pneumonia.—Lipoid pneumonia is a common post-mortem finding in milk-fed infants, but it seldom presents itself clinically. The inhalation of milk which may give rise to it is not uncommon in weakly infants, and the immediate treatment of this is bronchoscopic drainage, with postural drainage and full doses of penicillin and sulphonamides. The extension of a bronchitic process to involve the lung alveoli is probably preceded by blockage of bronchioles and collapse of small areas of lung, with subsequent infection, giving rise to diffuse lobular or broncho-pneumonia. This condition may be caused by any organism, but again the staphylococcus is the most common in the newborn.

The story in infancy is that of a baby who gets a cold which affects his chest, and who, instead of throwing it off in a week or so, becomes progressively more ill and develops areas of dullness with patches of crepitation and bronchial breathing throughout the chest. The differential diagnosis from an acute asthmatic attack may be difficult, but the presence of many musical rhonchi should lead one to suspect asthma. The treatment is the same as for pneumococcal pneumonia, but the prognosis is not so good.

OTHER LOWER RESPIRATORY DISEASES

Collapse of lung.—This is a frequent complication of any upper or lower respiratory infection in this age-group. It is diagnosed radiographically after finding physical signs resembling either those of fluid or consolidation. A shift of the mediastinum towards the side of the collapse which can be made out clinically is rare in infants.

If the child is not febrile, and there is no reason to suppose that the col-

lapsed area is infected, treatment should be directed solely towards getting the lung to re-expand. Frequent changes of posture, tipping the baby over the knee, and firmly clapping the chest wall several times daily usually result in re-expansion; but if this fails, bronchoscopic aspiration of the obstructing mucous plug should be done early, before the collapsed lung becomes grossly infected. After the lung has become infected, the same efforts to get it to re-expand must be made, coupled with treatment as for pneumonia.

Obstructive emphysema.—Sometimes when a mucous plug partially, but not completely, blocks a bronchus, air can be inspired past the obstruction but cannot be expired again because of the weakness of the expiratory effort. This can occur with or without obstructive collapse, but when massive, will cause collapse of lung by pressure, with mediastinal shifting, and cardiac embarrassment. The physical signs are a blowing out of one side of the chest, with a tympanitic note over it and a diminished air entry, but these signs are only present in the most extensive cases. The minor degrees will respond to the expectant treatment of collapse, but in the extensive case, removal of the plug by bronchoscopy may be necessary.

Pneumothorax.—This is not an uncommon finding in new-born babies with a little respiratory embarrassment. In such cases it quickly absorbs spontaneously and the only treatment necessary is oxygen for the respiratory embarrassment. When, however, it complicates neonatal pneumonia, it may be caused by the rupture of a small staphylococcal abscess and be accompanied by an empyema; then the treatment is the same as for empyema.

Empyema.—Chaplin (1947) has shown that in infants, staphylococcal empyemas are at least as frequent, if not slightly more frequent, than pneumococcal. These infections occur in the neonatal period and are then a manifestation of neonatal sepsis. In older children they are a complication of pneumonia.

Repeated aspiration of the pleural cavity, using local anæsthesia and a wide-bore needle, and replacing the fluid withdrawn by a solution of penicillin of slightly less volume containing up to 50,000 units, combined with systemic sulphonamide and penicillin in full doses, is the initial treatment. In some cases, about half, no other treatment is needed, but when the pus becomes thick and cannot be aspirated, an intercostal catheter may have to be introduced, and later more extensive surgical drainage with breaking down of loculations may have to be done. Aspiration treatment is controlled by repeated X-rays to assess the amount of pus remaining after each aspiration. Again, the organism must be looked for at the first aspiration and its sensitivity to sulphonamides and penicillin ascertained. The other antibiotics may be used if a resistant organism is found.

Whooping-cough.—The mortality rate from whooping-cough is greatest under the age of one, but is still high between one and two. Although inoculation with a reliable vaccine of "phase B" *Hæmophilus pertussis* holds out some hope of immunity when given at a very early age, results in this

cases, was somewhere between 10 and 30 per cent. The mortality of broncho-pneumonia was always higher, but in the under-two age-group this difference was not so marked. With penicillin and sulphonamides both mortality rates have been greatly reduced, that of lobar pneumonia now being around 5 per cent. Therefore penicillin and sulphonamides should both be given in full doses to children with lobar pneumonia. An oxygen tent (or box) for cyanosis, and brandy in doses of 5 to 10 minims (0.3 to 0.6 ml.) for circulatory failure, constitute the treatment. Penicillin and sulphonamides should be given until the temperature, respiration rate and pulse have been normal for three days; usually they fall dramatically within the first forty-eight hours.

As Chaplin (1947) has shown, the complication of *empyema* in infants due to pneumococci and streptococci has become much less frequent since the introduction of penicillin and sulphonamides, but hardly any reduction has occurred in the incidence of staphylococcal empyema.

The frequency with which *otitis media* complicates pneumonia in infants makes regular inspection of the drums a necessity. It is a frequent cause of sustained temperature after forty-eight hours of treatment.

(2) *Aspiration Pneumonias*

Inhalation pneumonia.—Lipoid pneumonia is a common post-mortem finding in milk-fed infants, but it seldom presents itself clinically. The inhalation of milk which may give rise to it is not uncommon in weakly infants, and the immediate treatment of this is bronchoscopic drainage, with postural drainage and full doses of penicillin and sulphonamides. The extension of a bronchitic process to involve the lung alveoli is probably preceded by blockage of bronchioles and collapse of small areas of lung, with subsequent infection, giving rise to diffuse lobular or broncho-pneumonia. This condition may be caused by any organism, but again the staphylococcus is the most common in the newborn.

The story in infancy is that of a baby who gets a cold which affects his chest, and who, instead of throwing it off in a week or so, becomes progressively more ill and develops areas of dullness with patches of crepitation and bronchial breathing throughout the chest. The differential diagnosis from an acute asthmatic attack may be difficult, but the presence of many musical rhonchi should lead one to suspect asthma. The treatment is the same as for pneumococcal pneumonia, but the prognosis is not so good.

OTHER LOWER RESPIRATORY DISEASES

Collapse of lung.—This is a frequent complication of any upper or lower respiratory infection in this age-group. It is diagnosed radiographically after finding physical signs resembling either those of fluid or consolidation. A shift of the mediastinum towards the side of the collapse which can be made out clinically is rare in infants.

If the child is not febrile, and there is no reason to suppose that the col-

Fluids.—Any infant with a respiratory infection is likely to be dehydrated by concomitant diarrhœa and vomiting, and this must always be corrected by extra fluid by mouth, if this is possible, or subcutaneously or intravenously. This is particularly important when large doses of sulphonamides are being given, if crystalluria and its complications are to be avoided. Upon the whole, the more soluble compounds, sulphamezathine or sulphatriad, are preferable in such cases.

PROPHYLAXIS

Although many studies of the effect of prophylactic *sulphonamides* upon respiratory and rheumatic infections in older children are available, few cover this age-group. It has been found in day nurseries, however, that daily doses of 0.25 to 0.5 g., according to age, will cut down the incidence of respiratory infections, presumably by cutting down the secondary infection, for it cannot help the virus coryzas. Similar studies using a buffered tablet of 50,000 units of penicillin by mouth have been done. It seems doubtful, however, because of the prevalence of *Staphylococcus aureus* in this age-group, and because this organism is so often found to be resistant to penicillin and sulphonamides, if this treatment should be used in a closed community.

Mackay and her colleagues (1946) have shown in a series of studies in day nurseries that a rise of hæmoglobin of the order of 6 per cent. was accompanied by a reduction of 20 per cent. in the absentee rate. They conclude that the anæmia affecting these children was nutritional and correctable by *iron therapy*, and that the prophylaxis of anæmia in day nursery infants was capable of producing a striking reduction in the morbidity rate.

In infants with second-class respiratory mucosa, who are particularly likely to have respiratory infections, it is wise to double the ordinary dose of *cod-liver oil* because of the possibility that vitamin A may, in increased doses, help them to avoid repeated infection.

Lastly, there is a group of children within this age-group who are particularly liable to respiratory infection. These are premature infants in the first two years of life, other small birth-weight babies, infants with rickets, coeliac disease, and cystic fibrosis of the pancreas, but in addition to these, there are infants with second-rate respiratory mucosa who suffer from none of these diseases, but get every infection that is going. All these children should be given iron and increased vitamins A and D.

References

- Chaplin, A. E. (1947): *Arch. Dis. Childh.*, **22**, 91.
 Field, C. E. (1949): *Pediatrics*, **4**, **21**, 230, 355.
 Mackay, H. M., et. al. (1946): *Arch. Dis. Childh.*, **21**, 145.
 Moncrieff, A. A., and Weller, S. M. V. (1949): *Lancet*, **ii**, 748.
 Morgan, E. E., and Wishart, D. E. (1947): *Canad. med. Ass. J.*, **56**, 8.
 Moseley, T. H. (1948): *Arch. Dis. Childh.*, **23**, 93.
 Scadding, J. G. (1946): *The Practitioner*, **157**, 333.

country have not yet shown the success that has been reported in America. The disease must be suspected in any infant with a spasmodic cough and vomiting, with or without a contact history. A cough plate will clinch the diagnosis in the early stages, and a lymphocytosis up to 30,000 is corroborating evidence. Sometimes the organism can be recovered by causing a cough by tickling the back of the pharynx with a camel-hair brush and plating the result. The mortality of this disease is largely from the complication of aspiration pneumonia, so that a good case can be made out for prophylactic use of penicillin and sulphonamides in the early stages of the disease in infants.

In any child who has a recurrent whooping-cough-like cough, especially when this is associated with diarrhoea, cystic fibrosis of the pancreas should be suspected.

TREATMENT

SULPHONAMIDES	PENICILLIN
2 grains (0.13 g.) per lb. (0.3 g. per kg.) body weight daily, divided into aliquot doses at four- to six-hourly intervals throughout the twenty-four hours, with twice this amount as the initial dose.	<p><i>By mouth</i>, 20,000 units per lb. (44,000 units per kg.) body weight per day, given upon an empty stomach at four-hourly intervals.</p> <p><i>By intramuscular injection</i>, 4000 units per lb. (8,800 units per kg.) of body weight per day, divided into aliquot doses at four- to six-hourly intervals throughout the twenty-four hours.</p>

Moseley (1948) and others have found that this oral dosage will give adequate blood levels of penicillin in infants under the age of six months, over that age the blood levels are capricious because of differences of absorption. The oral route is only contraindicated in babies under six months when there is vomiting. The antibiotic is best given in freshly prepared solution of high concentration by teaspoon.

Other antibiotics.—These may be used in cases in which the organism is found to be penicillin- and sulphonamide-resistant.

Streptomycin, 0.02 g. per lb. (0.044 g. per kg.) body weight daily, divided into aliquot doses given intramuscularly six-hourly.

Chloromycetin, 0.05 g. per lb. (0.11 g. per kg.) body weight, every three hours by mouth.

Aureomycin, 0.005 g. per lb. (0.011 g. per kg.) body weight, every six hours by mouth.

Chloromycetin and aureomycin are dispensed in capsules, the contents of which may be turned out and suspended in water or mucilage for administration by mouth.

be sterilized but the multiple foci in the depths of the tonsils and the lines of extension from these to the neighbouring tissues. Systemic penicillin is thus essential, and to ensure that the material penetrates rapidly the preliminary dosage should be large. The initial injection should be of the order of 200,000 to 500,000 units (dependent upon age), and this dose may be repeated six to eight hours later. Subsequent therapy may be based upon the efficacy of the original dosage; should this have been clinically very apparent, a daily dosage of 500,000 units, in two or three injections, will suffice; in the more severe cases, in which perhaps invasion of the middle ear or of the nasal sinuses has occurred, a high dosage is desirable for two to three days. Penicillin therapy should be continued for at least five, and preferably for seven, days. For such a severe case to have occurred suggests either an enhanced invasiveness of the infecting organism or an impoverished resistance on the part of the host, and these indicate a need for continuing treatment. For similar reasons penicillin in oil should not be used for the early, more urgent stage of treatment when the need is to supply the maximum effect rapidly. Such forms of penicillin may have a place in the continuing stage once the acute symptoms have been brought under control.

Many other less common forms of sore throat benefit from the use of penicillin. The diagnosis of *Vincent's infection* may be suspected because of its less acute onset and appearance. Here infection is not confined to the tonsils, and the greyish membrane which forms the floor of the shallow ulcers will often be found in small linear patches on the posterior pharyngeal wall. Further, although not constant, an accompanying gingivitis is common since the condition usually affects the whole oral cavity. In such cases penicillin must be used with caution. It seems likely that one of the factors which encourages a Vincent's infection is an imbalance of the healthy distribution of the normal mouth flora. The administration of penicillin may further upset the balance by killing off the gram-positive organisms and thereby encouraging a predominantly gram-negative flora. For this reason the milder cases should be treated by means of a local paint, such as neoarsphenamine (2½ per cent.) in glycerin, and the condition be observed for twenty-four hours. Careful attention to oral hygiene, frequent mouth washes, especially after food, and the application of the paint to the gums and small ulcers will often induce rapid healing, without recourse to penicillin. For the severe case with extensive ulceration, however, penicillin will be essential. Topical application is here quite justified, for the infection is essentially localized to the mouth. When treatment is started one or two large intramuscular injections may be given, but thereafter lozenges prove adequate for almost all cases. The patient should be seen each day and penicillin stopped when a beneficial local effect is noted. Prolonged treatment is undesirable for it may itself induce stomatitis, of which the patient may find the raw, sore tongue as troublesome as the original infection. During treatment the administration of a vitamin B compound may lessen

THE USE AND ABUSE OF PENICILLIN IN RESPIRATORY INFECTIONS

BY 'THOMAS ANDERSON, M.D., F.R.C.P.Ed., F.R.F.P.S.

Lecturer in Infectious Diseases, University of Glasgow; Physician, Knightswood Hospital.

So much has now been written on the place of penicillin in the therapy of the different acute infections that it might seem almost unnecessary to add yet another article. None the less, to take stock of one's experience from time to time is always of value, for it may thereby be possible to cast aside that which is based on theory rather than on practice. At the beginning of another winter season, when there will be the usual increased prevalence of respiratory infections, a survey of the ways in which penicillin may usefully be employed in their management is thus worth while.

UPPER RESPIRATORY TRACT INFECTIONS

Acute tonsillitis or *tonsillo-pharyngitis* is by far the most common infection of the respiratory tract. In over one-half of the cases the responsible pathogen is *Str. pyogenes*: the remainder have a somewhat diverse etiology, although it is likely that a virus or group of viruses is responsible for the greater proportion. If tonsillitis is the most common infection it is also as a rule the mildest, and consequently the use of penicillin, whether locally or systemically, for the routine treatment of the ordinary, non-exudative and uncomplicated infection is quite unjustified. The majority of cases make a rapid and straightforward recovery without unnecessary interference. The presence of a confluent exudate with considerable œdema of the fauces and soft palate is usual in the severe streptococcal infection, and in such cases further invasion to neighbouring structures must be anticipated. Cervical adenitis, reddening of the ear drum, or development of pain over the paranasal air cells will each suggest an extension of infection and the need for immediate institution of penicillin therapy. In other words, the decision to use penicillin in such cases is based upon the clinical observation that the infecting pathogen is beating the defences of the host. Such an outcome is usually noted early in the infection and it is therefore important to include ears and sinuses in the initial examination.

For such cases it might seem that the need for a high local concentration of the antibiotic was best met by local treatment, for example, by lozenges or tablets to be sucked. This view, however, fails to take account of the fact that in this type of case it is not the surfaces of the tonsils which require to

for which penicillin is preferable.

(1) Although the pneumococcus is by far the most common pathogen, the possibility of other organisms must be kept in mind. During recent years the staphylococcus has become more important as a cause of pneumonia, particularly when it occurs as a complication of influenza. As a rule the onset is less sudden, the consolidation less well-defined and diffuse, and the sputum is usually frankly purulent. Arising after a day or two of influenzal

TABLE I

COMPARISON OF RESULTS OBTAINED WITH SULPHATHIAZOLE AND/OR SULPHADIAZINE AND PENICILLIN BY ANY ROUTE IN PNEUMOCOCCAL PNEUMONIA

	Sulphonamide	Penicillin
Total cases	290	210
Total deaths	21 (7.2 per cent.)	17 (8.1 per cent.)
Cases with bacteraemia	51 (17.6 per cent.)	44 (21 per cent.)
Deaths in bacteraemic cases	11 (21.5 per cent.)	12 (27.4 per cent.)

symptoms the condition of the patient may become profoundly changed almost in a matter of hours. The general signs of toxæmia are usually well marked. For such cases penicillin, which should be given in massive dosage, may well prove life-saving. One of the features of staphylococcal pneumonia is the frequency with which empyema occurs. The possibility of such a complication must be remembered, for it will require not only systemic but also intrapleural penicillin.

The importance of staphylococcal pneumonia in infants is worth particular mention for, at least in hospital practice, it has become much more frequent in the last few years. At this age-period the pneumonia usually seems very extensive and is often lobar in distribution. Here too, empyema is a frequent early complication and, since it probably arises as a result of the rupture of a subpleural infarct, penicillin should be given with abandon and by both intramuscular and intrapleural routes.

(2) The two factors of greatest significance in prognosis are age and the presence of bacteraemia. The diagnosis of pneumonia in a patient over the age of forty years should always be regarded as an emergency demanding intensive therapy. In older persons, too, the past history may reveal the presence of some chronic cardiac or renal disease, the presence of which tends to deter the clinician from using the sulphonamides in adequate dosage. The lack of toxicity of penicillin is a great advantage in these circumstances and, during the first twenty-four to thirty-six hours, a total dose of 1.0 to 1.5 mega units may clear the infection without danger to the

the risk of glossitis.

Agranulocytic angina is another rather uncommon throat infection for which systemic penicillin proves effective. The appearance of the throat in such cases bespeaks the lack of resistance of the host, for there is an absence of those signs of acute inflammation which such an extensive ulceration would lead one to expect. The patient is usually an adult, and in most cases there is a long history of the taking of some form of analgesic tablet. The value of penicillin here lies in its freedom from toxicity, and adequate amounts should be given systemically. Apart from the administration of pentnucleotide, all other forms of drug therapy should be omitted. As a rule, the rise in the white cell count is a reflection of the controlling of the infection and in my own experience has borne little relationship to the administration of the pentnucleotide. In severe cases blood transfusion should be considered.

Diphtheria, although quite clearly a respiratory infection, has diminished in importance in recent years, partly as a result of the extensive practice of active immunization of children and partly from a decreased prevalence of the infection. Nevertheless, one form—*laryngeal diphtheria*—is so often associated with spells of intense cold weather that it should be emphasized as a "winter risk". Diphtheria antitoxin is of course a prime necessity. But, particularly in this laryngeal form, penicillin has a valuable place in therapy, and there is every reason to believe that its use, in high dosage, will lessen the need for tracheotomy. In tonsillar infections the administration of penicillin during the first week hastens the disappearance of organisms. Diphtheria bacilli are relatively resistant to penicillin and to some extent sheltered from its action, so that high dosage is essential.

PNEUMONIA

Pneumonia is by far the most important of the respiratory tract infections, and in the great majority of cases has a pneumococcal basis. One of the fundamental questions with which the physician is faced is what therapeutic substance to use in the management of a case. Many considerations may have to be taken into account, but when a straightforward comparison is made of patients treated with sulphadiazine or sulphathiazole with those given penicillin it is abundantly clear that there is little difference between them. The results shown in table 1 have been obtained in the same hospital during the last few years. Both in the routine cases and in the more severe cases with bacteriæmia the results obtained with the two substances are essentially similar. This is important in the management of cases in general practice, for whereas sulphonamide can be administered with comparative ease, the giving of penicillin may be somewhat difficult. Accordingly, the results shown in table 1 give good grounds for advising that in the straightforward case sulphonamide will prove adequate. Having made this statement, however, attention may be directed to four main groups of cases

to be stressed is that in the early dangerous stage penicillin instillation may be life-saving by diminishing the toxic absorption. The patient may thus be tided over until an operation can be undertaken with safety.

MODE OF ADMINISTRATION IN PNEUMONIA

When the decision has been taken to use penicillin it may be argued that the immediate need, in such an ill patient, is to secure as rapidly as possible a high concentration of the antibiotic, both systemically and locally. For this purpose the use of a large dose of the aqueous solution seems best. The "depot" effect of penicillin-in-oil seems less important, although it is no doubt adequate for the straightforward case. It has yet to be shown that the steady achievement of a certain amount of penicillin in the blood stream is actually essential, especially in such infections as pneumonia, when there is no doubt that man's basic resistance to the common invading pathogen is good. It seems possible that there may be some advantage in the waxing and waning of the blood level of penicillin which occurs after the injection of aqueous solutions by allowing the growing out of new generations of organisms to be smitten by the next peak concentration. Orally administered, penicillin is also effective in the routine management of pneumonia; but in the light of the previous reasoning, once the decision has been taken to use penicillin for patients in the above categories, it is desirable that the initial treatment should be by intramuscular injection. Finally, although its administration by inhalation may secure adequate blood levels, in general use this method is cumbersome, is disliked by the patients, and may increase the risk of sensitization.

The administration of penicillin to patients with *chronic pulmonary infections* is often considered. Here it is of the greatest importance to make a planned approach to treatment by securing a complete bacteriological examination of a carefully taken specimen of sputum. Looked at in the best possible light, penicillin is but a placebo in the majority of such cases. It may secure a rapid clearing of the penicillin-sensitive organisms, but the underlying chronic mucosal changes favour the occurrence of further reinfection as soon as the administration of penicillin is stopped. Permanent improvement is thus not usual. It may, however, be of great benefit during the acute exacerbations due to super-infection, which are such a frequent event in such cases. Penicillin has also a limited place in the preoperative preparation of cases for lobectomy or thoracoplasty. For the patient with chronic pulmonary infection, inhalation of an atomized solution is the best method of administration.

CONCLUSION

To have a clear mental picture of "how the wheels go round" may not be an essential, but it is certainly an important part of the proper management of a machine. In the use of drugs too, the physician often likes to have some

patient. Treatment thereafter may be continued with either sulphonamide or penicillin.

At least in hospital practice, a blood culture should always be made before treatment is begun. The presence of organisms in this initial culture indicates a severe infection, and when the result is known at the end of twenty-four hours, adequate penicillin therapy should at once be instituted.

(3) Although leucocytosis is usual in pneumonia, leucopenia or granulocytopenia occurs infrequently, indicating an intense infection with a poor host response. Agranulocytosis may also be encountered as a rare complication of sulphonamide therapy; much more frequently, however, previous administration of these substances has sensitized the patient so that a single dose produces a severe reaction. Although such cases are uncommon it is important to recognize them and to institute treatment with penicillin.

(4) Finally, the formation of pus in the pleural cavity during the acute stage of the illness (syn-pneumonic empyema) is a dangerous complication which may actually arise in the course of sulphonamide treatment. When the suspicion arises that pus may be present, aspiration must be carried out. If pus is obtained, a reasonable quantity (100 to 150 ml.) should be removed, and penicillin (0.5 to 1.0 mega units in 10 to 20 ml. of distilled water) slowly injected. With an ill patient no attempt should be made to empty the cavity at this first aspiration, and precautions should be taken to prevent the entrance of air to the cavity by using a two-way tap. On the following day the procedure should be repeated, but this time an attempt should be made to take away as much pus as possible, again instilling 500,000 units of penicillin as the last procedure. Such measures will tide the patient over the most serious stage of the illness and will permit a more planned approach to operative interference. Needless to say the pus must be subjected to a careful bacteriological examination to determine the type of organism and its sensitivity to penicillin. When empyema develops in a patient who is not receiving penicillin, it is important to start such treatment at once in order to bombard the collection of pus from both sides.

Although the general principles of the use of penicillin in such cases may be thus simply stated, it would be a pity if the impression were given that the whole management of the patient with an empyema can be so lightly dismissed. In the first place, it must be emphasized that no two cases are exactly alike, so that to prescribe a "routine" is dangerous. These patients will require skilled management, and it is desirable that the thoracic surgeon should be consulted at an early stage. Frequent X-ray examination will be necessary to observe the progress of the cavity, and lipiodol intrapleurally may be useful in this respect. My own experience has been that for small, well-localized empyemas, penicillin therapy followed by the introduction of an intercostal drain usually proves adequate. With large effusions such a method may fail and early rib-resection then becomes essential. The point

OXYGEN THERAPY

By IAN G. W. HILL, C.B.E., M.B., F.R.C.P.Ed., F.R.S.E.

*Assistant Physician, Royal Infirmary, Edinburgh; Lecturer in Therapeutics,
University of Edinburgh.*

IN reviewing the topical aspects of oxygen therapy two striking changes that have occurred in the last decade must be recorded. These are the decline in the prejudice of patients against the use of oxygen, and the greatly increased availability of modern and efficient apparatus for its administration. Twenty years ago, even in large hospitals, oxygen was reserved too often for the desperately ill patient *in extremis*, and was rarely used outside hospital. There was more than a grain of truth in the well-worn quip that the cab bringing the oxygen cylinder was the herald of the undertaker. Since the arrival of the apparatus was an omen of the direst significance to patients, it was natural that doctors should delay the use of oxygen in the hope of sparing anxiety, with the result that its inhalation, which given earlier might have been life-saving, was restricted to practically the agonal gasps of desperate cases. To-day, recognition of the value of oxygen, like that of blood transfusion, is widespread among lay people, and its general use in early non-fatal cases has established confidence where before dread prevailed. Lay familiarity with the advantages of oxygen has run parallel with increased technical proficiency in its use, so that it is rare indeed now to find someone using the old tube and funnel, or cutting off the supply for some fraction of each hour as was customary in the past. Again, since 1939, efficient apparatus has been installed in a host of small hospitals, and in many larger institutions oxygen is piped to each bedside in the wards, so that it is available for any patient, promptly and with a minimum of fuss.

METHODS OF ADMINISTRATION

Apparatus.—For efficient administration the rate of discharge from the cylinder must be controlled by a fine-adjustment valve and measured by a reliable flow-meter, whilst the delivery to the patient must ensure that the gas reaches his lungs in adequate concentration. Between the cylinder and the fine-adjustment valve a reducing valve is interposed, bringing the very high pressure of the gas in the reservoir down to manageable levels. The fine-adjustment valve generally consists of a needle bearing on an accurately ground seat, the needle being raised by a micrometer screw to allow the gas to escape. It is important that this construction be kept in mind, so that the needle is not damaged by careless or forcible use of the screw. When the gas is to be turned off the main valve on the cylinder should be closed with the key, and no attempt made to stop the flow by screwing the fine-adjustment valve hard down.

The use of a wash-bottle containing warm water, with a delivery tube

image in mind which, without over-simplifying the problem, helps him to understand their mode of action. As a generalization it is perhaps true to say that many of us imagine chemotherapy very much as a test-tube experiment—the addition of so much chemical to so many micro-organisms with their resulting subjection. When this analogy is applied to the use of the substance in man, however, it leaves out of account all of the variables that are a part of human infection. The host's previous experience of different bacteria and his capacity to defend himself against them; the variation from organism to organism in its ability to invade the tissues of the host; the varying susceptibility and the accessibility of the pathogens to the substance administered: factors such as these make the application of the chemical to disease in man demand an understanding not so much of its precise mode of action as of the nature and course of the infection to be treated. So in considering the use of penicillin in infections of the respiratory tract little emphasis has been placed on a knowledge of the sensitiveness of different bacteria, or of the concentration desirable for their control. Such information, whilst important, takes almost second place to a clear understanding of the nature of the "host-parasite" complex which forms the basis of any acute infection. The therapeutic efficiency of penicillin is so great in those infections which were previously fatal that we are sometimes inclined to forget that in many other infections it acts as an adjuvant to man's own capacity to recover. There is little doubt that the most serious abuse of this potent substance is the tendency to use it more because of the reading on the thermometer than on an appreciation of what we expect it to do. The dosage, the route of administration and the duration of treatment will depend to a large extent upon a knowledge of the mode of attack of the organism.

The extent to which a proper bacteriological diagnosis is essential can be overemphasized. It would no doubt be a policy of perfection to make an adequate bacteriological examination in all cases, but such advice is scarcely practical. There are many clinical diagnoses of respiratory infection which incriminate a particular pathogen with some degree of certainty. In such cases the clinician will be fully justified in beginning treatment without further delay. Nevertheless, it must be remembered that the susceptible acute infection shows a rapid response to penicillin therapy, usually indeed within twenty-four to forty-eight hours. This will serve as a valuable indication of the efficacy of treatment and a good reason for its continuation. Perhaps of more importance is the failure to observe improvement in such cases. No time must be lost in making a careful appraisal of the situation. The necessary specimens should be submitted to ascertain if the cause is unusual; the original diagnosis should be reviewed; and the method of administration and the amount of penicillin administered should be reconsidered.

patient, to avoid any sensation of restricted breathing or suffocation. Supervision of the administration is desirable with any form of inhaler, ensuring that the flow is adequate, the fit of the facepiece and its application satisfactory, and the patient comfortable. With the B.L.B. mask running properly the bag is fairly fully distended in expiration and empties partially with each breath inhaled. An empty bag means inadequate flow and possibly a suffocating patient.

The fourth method of administration is by an *oxygen tent*. This consists of a fabric sheet supported on a wire frame, providing room for a patient to be nursed sitting upright, and furnished with large windows for the comfort of the inmate and to allow observation of his condition. The edges of the tent are tucked under the mattress, and a free flow of oxygen admitted. Soda-lime extraction of water and carbon dioxide is essential, and a cooling device is an advantage. Such an apparatus is costly, but its advantages render its use an essential in certain types of cases (see p. 522). For young children and infants, who tolerate masks badly, an improvised tent can be made of canvas with X-ray film for windows, provided CO₂ content and humidity are prevented from rising by the use of soda-lime. Such tents are of great value in a children's ward.

OXYGEN REQUIREMENTS

To attain an adequate oxygen concentration in the alveolar air the rate of flow has to be considerably higher than is commonly realized. With the nasal catheter some 6 litres per minute are required to raise the alveolar oxygen to the desired level (40 per cent.). A similar concentration can be achieved with the B.L.B. mask with rather less, but still some 4 litres per minute are a minimal requirement. Rates of 2 litres per minute, such as are usual when the gas is bubbled through a wash-bottle in a rapid stream, are practically useless; and when a wash-bottle shows a succession of discrete bubbles the gas is merely being wasted.

In all conditions in which oxygen therapy is indicated *continuous administration throughout the period of need is imperative*. It is irrational and harmful to give it intermittently. The old practice of stopping the flow for, say, ten minutes in each hour has been aptly described as equivalent to "dispatching the patient to the top of Everest for a breather". Custom dies hard, and this habit of many senior nurses must be foreseen and countermanded.

SAFETY PRECAUTIONS

Familiarity breeds contempt, and precautions against accident should be impressed on all concerned in giving or handling oxygen. Lubrication of the high-pressure valves with oil may lead to fire, and is specifically forbidden by the manufacturers in legends on the cylinder leads. Fire may also occur through ignorance of the fact that high concentrations of oxygen cause a smouldering object to blaze fiercely, as should be familiar to all who have had a training in elementary chemistry. A cigarette or match carelessly

perforated by a series of holes, has long been customary, with the idea that the gas may be warmed and moistened, and the rate of flow gauged. Actually with the rates of flow (4 to 8 litres per minute) now known to be necessary, turbulence in such a bottle is very great, and there is considerable risk of blowing water into the delivery tube. A dry bobbin-type flow-meter, of the type common on anæsthetic machines, carries no such risk, and being at the same time much more accurate is greatly to be preferred. Such a flow-meter can be obtained complete with reducing valve and fine-adjustment valve in a single fitting which screws into the cylinder head.

* *For delivery to the patient* there is a choice of simple and efficient methods. The simplest and most easily improvised in emergency is a *simple nasal catheter*: a soft rubber tube (catheter size 9), lubricated with jelly containing benzocaine, is passed back along the floor of the nose to the posterior pharyngeal wall, and then withdrawn half an inch. The catheter is connected to the delivery tube from the flow-meter, and fixed to the forehead by adhesive tape, or by a band of the type used for a forehead mirror. It should not be stuck to the cheek with adhesive tape, and should not be fixed to the pillow in such a way that movements of the head may drag it from the nose.

The *Tudor-Edwards "spectacle-frame"* is a modification of this method. In it, narrow metal tubes run from the temple below the eyes and down from the bridge of the nose to each nostril, where they end in recurved short uprights and fit inside the nose. In use these terminals are sheathed with fine rubber tubing (e.g. bicycle valve-tubing) which projects $\frac{1}{4}$ to $\frac{1}{2}$ an inch beyond the metal into the nose and is suitably lubricated. The spectacle frame is more comfortable for the patient than the catheter, and since the delivery tube is double, a higher rate of flow can be tolerated than when a single tube delivers a fast jet into the nose.

A third somewhat more elaborate method is the use of the *B.L.B. mask*. The distribution of this apparatus to civil and military hospitals during the war was so wide that there must be few practising doctors in this country who are not familiar with it. Two forms of facepiece are in use, both of soft rubber, and secured by a simple head-harness. In one, the mouth and nose are covered as in the old Haldane apparatus; in the other the mask fits over the nose only, leaving the mouth exposed and allowing the patient to breathe orally if he so desires: this tends to minimize the feeling of suffocation which some apprehensive patients experience when mouth and nose are both enclosed. Below the mask hangs a bag, which acts as a reservoir. Oxygen is delivered into the bag through the connecting tube between bag and facepiece, and the apparatus is fitted with appropriate valves so arranged that on inspiration the patient inhales the contents of the bag, and on expiration exhales into the air. In some models the connexion has a sliding collar which can be rotated to allow of entry through a series of ports of a variable quantity of air to mix with the oxygen. This apparatus is probably the most satisfactory for general use. It is important that the oxygen should be turned on freely before the facepiece is applied to the

danger period until antibiotics or chemotherapy have dealt with the infective element. In chronic heart failure due to pulmonary disease oxygen is still of value but its continued administration may not be feasible.

The sudden onset of *massive pulmonary embolism*, if not at once fatal, throws a great strain upon the heart and pulmonary circulation, probably associated with a severe degree of spasm of the remainder of the pulmonary arterial tree. In such cases collapse and cyanosis are the rule, and oxygen in high concentrations is of great value in relieving respiratory distress and improving the condition of circulation.

In conditions of *shock*, whether following bodily trauma or in such a medical catastrophe as massive coronary occlusion, administration of oxygen is of value. Since in simple shock the pulmonary ventilation and aeration of the blood are unimpaired, oxygen in the usual concentration has little effect in raising the arterial oxygen saturation, the red cells being already fully oxygenated. By raising the alveolar oxygen concentration to high levels (around 90 per cent.), however, the partial pressure of the oxygen in the alveolar air is much increased, and diffusion into the plasma facilitated. In *massive coronary occlusion* some degree of left heart failure, with early pulmonary œdema, may develop and oxygen administration is still more essential. There is little doubt from experience that such high oxygen concentrations are of great value in otherwise desperate cases of coronary occlusion. To secure an adequate concentration in the lungs the gas must be supplied at high rates of flow—some 6-7 litres a minute by B.L.B. mask; it is not feasible to attain the requisite level with a nasal catheter.

In *carbon monoxide poisoning* oxygen therapy is also of utmost value. The affinity of the hæmoglobin for carbon monoxide is such that inhalation of even a low concentration of the poison leads to conversion of all the blood pigment to the carboxy form. This compound of hæmoglobin with carbon monoxide is very stable in air, and thus does not dissociate readily even when the subject is removed from the contaminated atmosphere to breathe fresh air. In the presence of high concentrations of oxygen, however, dissociation is facilitated, and inhalation of oxygen is thus a powerful remedy in such cases of poisoning. The B.L.B. mask is preferable to the catheter for administration in view of the ease with which high alveolar concentrations of oxygen are attainable.

THORACIC SURGERY AND OXYGEN THERAPY

Radical surgical intervention within the thorax is now no longer rare, and specialized units all over the country are dealing daily with cases previously regarded as beyond the scope of surgical treatment. Lobectomy for lung cancer or bronchiectasis, thoracoplasty in tuberculosis, operations for œsophageal or high gastric neoplasm or ulcer, and thymectomy for myasthenia gravis, are all standard procedures. During the last few years the various operations for relief of congenital heart disease (ligation of the patent ductus, resection of aortic coarctation, and Blalock's or Pott's opera-

handled may thus start a fire, and smoking near a patient receiving oxygen should be forbidden.

INDICATIONS

Oxygen inhalation is unlikely to benefit a patient in whom pulmonary ventilation and circulation are adequate to secure full oxygenation of the blood leaving the lungs. Thus in anæmia with normal heart and lungs what hæmoglobin there is, is fully oxygenated in the lungs, and oxygen inhalation will not raise the content in the arterial blood. Again, a patient with congenital heart disease and deep cyanosis may benefit little from the gas, if the cyanosis is due to a venous-arterial shunt and not to defective oxygenation of the blood in the pulmonary circuit. So also the patient with cyanosis due to peripheral stagnation and over-reduction of the blood in the extremities may fail to obtain relief from inhaling the gas. Again, dyspnœa is no absolute guide to the need for oxygen, for physiologically it is known that oxygen lack is not a strong stimulus to respiration, and a severely anoxic patient may not be short of breath. On the other hand, cardiac dyspnœa is caused by a complexity of factors of which oxygen lack is not the chief, and oxygen therapy may fail to abolish such distressed breathing. These considerations should be borne in mind in deciding for or against the employment of oxygen, to avoid misuse and consequent disheartening failure.

The inhalation of oxygen is probably of maximal value in cases in which the gaseous interchange in the lungs is impaired, so that the arterial blood in the pulmonary veins and left heart is sub-oxygenated. For example, diffusion may be hindered by the inflammatory exudate of *pneumonia* or *capillary bronchitis*, or by the watery film that gathers in *pulmonary œdema*. Such pulmonary œdema developing suddenly in an attack of cardiac asthma may threaten life in the course of half an hour. Patchy or massive *atelectasis* may throw a large proportion of the lung out of use; shallow, rapid respiration may result in faulty ventilation of the alveoli: intense pulmonary congestion may cause overcrowding of distended capillaries in the alveolar walls, so that diffusion from the air cells to the centre of the blood columns is imperfect. All result in some degree of oxygen unsaturation of the arterial blood and all may be improved by inhalations of higher concentrations of oxygen than the 20 per cent. normally present in the air.

In gross *emphysema* and in *pulmonary fibrosis*, maloxxygenation of the blood in the lungs occurs, possibly partly due to cutting down of the capillary blood-bed. Recent work on the hæmodynamics of *heart failure* in "*cor pulmonale*" indicates that the cardiac output is high in such cases, and the circulation through both systemic and pulmonary circuits accelerated. There may be other factors therefore, apart from simple capillary bed defect, which lead to the characteristic cyanosis in these cases. In acute attacks of failure in *cor pulmonale* there is commonly a coincident respiratory infection (e.g. capillary bronchitis with patchy atelectasis) which increases the anoxæmia. In such crises oxygen administration is the most powerful therapeutic agent at our disposal in tiding the patient over the

PRACTICAL MEDICAL MYCOLOGY

A DISCUSSION OF SIMPLIFIED LABORATORY METHODS

By J. WALTER WILSON, M.D.

Assistant Professor of Medicine, Department of Dermatology, University of Southern California.

AND ORDA A. PLUNKETT, Ph.D.

Associate Professor of Botany, Department of Mycology, University of California, Los Angeles.

AMONG the forms of life too small to be seen with the naked eye, fungi, being comparatively large, were the earliest to be observed as parasites. In 1677, by using the crude hand lens available at that time, Hooke was able to point out that the disease occurring as yellow spots on rose leaves actually consisted of tiny living threads. As early as 1839 it was recognized that a fungus could be the etiological factor in a disease of animals when Schoenlein demonstrated and described the organism of favus in human beings, and three years later Remak reproduced the disease. Similar conclusive proof of the pathogenicity of other microscopic forms of life did not occur until Koch in 1876 and Pasteur in 1877 published their work on anthrax, marking the beginning of bacteriology as a science.

In spite of such early precedence, medical mycology has been far out-distanced by other similar sciences in popularity and scope. Not until the monumental work of Sabouraud, "Les Teignes", was published in 1910 was any noticeable momentum gained, and only during the last two decades has knowledge of mycology been extensively disseminated. Perhaps the principal reason for such delay lies in the fact there is no fungous disease which is both dangerous to life and of common occurrence, whilst among the diseases caused by bacteria several, such as plague, cholera and typhoid fever, formerly killed so many persons yearly that veritable crusades were organized against them. The study of fungi and the diseases which they produce could not be expected to attract adequate personnel until at least the easily discoverable answers concerning such scourges were known. It is difficult, however, to resist the temptation to point out that this degree of subjugation of mycology in favour of bacteriology almost certainly deprived the former science of many workers, some of whom might have discovered penicillin and streptomycin in less than the hundred years which history must record. The entire heavy metal phase of the therapy of syphilis might have been avoided. At present the greatest remaining unconquered field in microbiology concerns the difficult science of virology, in which it is apparent that significant discoveries will only be yielded after prolonged and intensive study. In comparison, mycology, because of its relative simplicity, now offers

tions for pulmonary stenosis and Fallot's tetralogy) have come into use in various clinics. Oxygen therapy plays a large part in the after-care of such patients, and for this purpose nursing in an oxygen tent of the type described on page 519 is practically essential. In such a tent the unhampered patient lives in an oxygen-rich atmosphere during his period of need, and any desired alveolar oxygen concentration is readily attained. In a properly equipped tent the humidity and CO_2 content and the temperature are controlled, and the patient is completely at ease, so that the stay in the tent can be prolonged to several days without hardship. The use of this tent is a very material factor in reducing the mortality of such operations, and all clinics undertaking such work should be fully equipped accordingly. It is well to ensure that at least one of the nurses on duty at any time is thoroughly familiar with the apparatus, and patients in tents must be kept under close observation. It is important to impress on all the staff that failure of the oxygen supply can convert the life-saving machine into an asphyxiating chamber. A reserve oxygen supply should always be at hand.

CEREBRAL THROMBOSIS IN MORBUS CÆRULEUS

An important indication for the administration of oxygen has recently been defined in the management of cerebral vascular thrombosis in cases of cyanotic congenital heart disease. Cerebral thrombosis in cases of severe *morbus cæruleus* is a well-known hazard to which such children are predisposed by the marked polycythæmia which accompanies deep cyanosis. Death from such thrombosis in a cerebral vessel was until recently looked upon as the natural termination in many cases. Now, however, when operations of the Blalock-Taussig type afford prospects of considerable betterment and prolonged survival in a proportion of cases, it is important to recognize and treat these accidents before irreparable damage is done.

Early symptoms or signs of a cerebral vascular accident in a deeply cyanosed child are an indication for prompt and vigorous treatment: (1) to reduce the polycythæmia, (2) to compensate for loss of hæmoglobin by supplying oxygen, and (3) to prevent further thrombosis by the use of heparin.

In practice the first step is a *small* venesection, only 20 to 50 ml. in an infant, or 100 to 250 ml. in a child of two to six years, depending upon the age and size of the child and the degree of polycythæmia. Oxygen therapy is started at once, the child being most conveniently nursed in an oxygen tent. An intravenous drip of saline or plasma is set up, in an attempt to dilute the blood, and heparin is added to the infusion fluid. A suitable dose is $\frac{1}{2}$ mg. per kg. of body weight, as an initial dose, and the same amount per hour in the drip. The coagulation time must be carefully controlled, and the treatment as a whole is a matter for a skilled hospital team of nurses and doctors.

The general practitioner, however, by early recognition and efficient handling, may either forestall serious damage or promote an amazing degree of recovery, even in cases with a frank, but recent, hemiplegia. The initial dose of heparin can be given and oxygen treatment by mask or nasal catheter started at once, while admission to a hospital is arranged.

should be removed by vigorous scrubbing with cotton saturated with 70 per cent. alcohol. Most of the bacteria, unimportant contaminating fungi, clots, crusts, pus, medicaments and other debris so often the cause of confusion can thus be eliminated. Any pathogenic fungi which are present as the cause of the disease in question will have penetrated the tissues more deeply and can still be recovered from an area cleaned in this manner. The specimen should consist of actual tissue; exudates such as pus or serum in vesicles will rarely suffice except in some of the deep mycoses. Generous portions should be removed; since fungi are larger than bacteria and not as densely packed in the tissues there may be none present in any particular fragment if it is small. Patients are anxious to cooperate when the purpose of this procedure is explained and rarely complain of the discomfort which it sometimes entails. At the same time similar portions of tissue should be used to inoculate cultures.

Most organic substances with which fungi might be confused when seen through the microscope will be converted by moderately strong solutions of alkali into an almost homogenous clear matrix with faintly visible cell outlines in which the unaffected fungi are easily demonstrated. It is best to use 10 to 15 per cent. potassium hydroxide for this purpose; stronger solutions act no more rapidly and often form crystals which may be confusing. A drop or two of this solution is added to the specimen on a microscopic slide and a coverslip placed over both. Some materials such as thin portions of epidermis or hairs should be first examined directly; they will often be found to be sufficiently transparent for adequate study without further treatment. In the case of hairs this method avoids unnecessary fragmentation of the shafts, allowing the position of the fungous elements in relation to them to be more easily discerned. Thicker portions of skin or hair insufficiently cleared need to be gently heated nearly to the boiling point; vigorous agitation of the specimen by boiling is detrimental since it may destroy all semblance of the original tissue. Portions from the sole and especially bits of nail must be subjected to prolonged and repeated heating, and enough time must be allowed for the necessary degree of chemical softening to occur so that the material may be pressed out into a sufficiently thin layer to afford good visibility.

When fungous elements are revealed in material properly prepared in this manner it may be concluded in most instances that the disease under study is of fungous origin. The differentiation between fungous and those non-fungous structures which might be confusing must depend upon a study of photographs which all good textbooks supply. In epidermal fragments it is not usually possible to determine the particular species of fungus present by direct examination except for *Candida* and *Malassezia*. In hairs one may be somewhat more certain. When a fungus is seen in material obtained from areas deep within the body tissues it is almost certain to be the cause of the disease. Whilst some of the deep mycoses lend themselves to conclusive

a most attractive field for research. The fact that after more than a hundred years there are no efficient therapeutic regimes for most of the deep mycoses and a large percentage of the superficial ones, is ample proof that much more detailed study will be necessary to discover them.

Several other factors which retarded the progress of mycology deserve discussion, principally because it is not generally realized that they have become controllable to such an extent that it is now easy for any practitioner to acquire whatever degree of mycological knowledge he may find of practical value in his chosen field. The complicated nomenclature and classification have been greatly simplified; the delineation between pathogenic and non-pathogenic organisms has been clarified; and simple, practical methods have been evolved for the direct examination of tissues, the culture and identification of the organisms and the preservation of specimens of teaching value. By reviewing these features briefly this article is intended to serve as an invitation to new students to enter this field, as well as to entice older practitioners to consider it again.

Differentiation between disorders of fungous and non-fungous origin on clinical grounds alone is highly inaccurate. This always becomes apparent whenever a community acquires for the first time the services of a practitioner interested in mycology; his laboratory work is able occasionally to reveal faults in diagnosis in the work of the most experienced clinicians and with higher frequency in those less qualified. After mycological study better treatment schedules may be selected and a much more accurate prognosis may be made. It is easier to gain and hold the patient's confidence if scientific mycological methods are employed.

To those who object to simplification because it introduces imperfections it may be pointed out that a simple formula in extensive use by large numbers of practitioners who are attracted to it will afford many more accurate diagnoses than precise complicated methods in the hands of those few individuals who possess the extensive mycological knowledge necessary to use them well. Such experts often fail to realize how easily they may cut themselves off from interesting material at its source: the physician who has charge of the patients. If he can be persuaded to use simple mycological methods for all patients he will seek the expert when he is puzzled and thus supply many more interesting oddities for interpretation.

DIRECT EXAMINATION

The simplest and most rapid method of ascertaining the presence or absence of a fungus in diseased tissue is to examine a representative portion of it directly under the microscope. The technique is easily acquired. There are several rules governing the manner in which specimens are obtained which should be closely followed. An area must be selected which is obviously active and typically involved in the pathological process under study; usually an acutely progressing border region is best. All extraneous substances

simply by throwing cultures which are no longer desired into the waste-basket after adding formalin to those which represent pathogenic fungi. A detailed discussion of many other advantages which this system affords would be too lengthy for the present article. Once this method is adopted it requires less time to inoculate cultures than to explain to patients that such a procedure is "unnecessary".

Choice of media.—Many different media have been advocated for the cultivation of fungi, some of which undoubtedly offer some advantages in the hands of the experienced mycologist. However, there is such a wide variation in the appearance of an organism when grown on different substrates that the average practitioner using several media is likely to become confused and fail to identify it. Too many such failures persuade him that the entire process is beyond his abilities and he abandons it entirely. It is much better that the vast majority of all mycology be taught and practised with reference to one simple medium. We advocate the use of Sabouraud's glucose agar with slight modifications. It consists of 1 per cent. peptone, 2 per cent. agar, and 4 per cent. glucose in water; ordinary drinking water should be used instead of distilled water so that some necessary salts will be included. We also like to use the glucose designated in the U.S. Pharmacopœia as "syrupy", because it has some desirable nutritional qualities lacking in more highly purified brands of glucose; since Weidman and McMillan (1921) and Weidman and Spring (1928) so adequately covered this phase of the subject, all experience has simply served to confirm their opinions. The brand of peptone (Difco Laboratories Co., Detroit) most commonly used for bacterial culture by bacteriologists in this country is also satisfactory for the preparation of this medium. Adjustments in pH will be necessary only in communities where water is highly alkaline. The pH should not be above 6.5 and may be brought to this level by the addition of sufficient lactic acid. Chemicals and antibiotics designed to inhibit bacterial growth are not desirable since some fungi will also probably be inhibited or at least changed in their characteristics so as to be recognized only with difficulty. Especially to be condemned for routine work is the use of dyes or other coloured substances in the medium, since the colour of gross colonies of fungi is important as well as the pigment which many species diffuse into the substrate. If the specimens for inoculation are taken carefully in the manner described earlier in this article there is no need for the inclusion of bacterial inhibitors in the medium. It is only when a specimen is teeming with bacteria and contains little or no visible fungous elements that the latter fail to make themselves known. It is well to reiterate the great importance of thorough cleansing of the area before selecting the specimen, and that generous portions of actual tissue should be taken.

There are only two pathogenic fungi which cannot be isolated routinely on this simplified medium when held at ordinary room temperature. *Actinomyces bovis* requires anaerobic conditions, and when it is suspected

diagnosis by this means alone, it is preferable to confirm it by subsequent culture since some do not. The diagnosis of sporotrichosis, for example, can seldom be established without culture.

CULTURE METHODS

The determination of the exact genus and species of fungus involved in a pathological process is often of great value as a guide to treatment; it is even more important in prognosis. In dealing with infections of the skin due to *Trichophyton rubrum*, for example, it is much easier to retain the patient's confidence throughout the necessarily prolonged period of treatment if he is acquainted soon after he is first examined with the difficulties to be expected. Parents who understand the significance of the discovery that *Microsporon audouini* is the cause of their child's tinea capitis are much better prepared for the long therapeutic battle which ensues. Many other similar examples could be cited; in fact, we believe that accurate identification of the organism is helpful to a certain degree in all fungus infections. This information can only be obtained through culturing the organism on artificial media.

Culture methods are, however, even less frequently employed in clinical practice than is the direct examination for fungi. There is widespread belief that such methods are extremely complicated and difficult, whereas they are really very simple. All essential features in the technique are easily learned. We have recently (1949) suggested a culture method which it is believed eliminates all

unnecessary complications. A square, flat, heavily reinforced glass bottle of 1/2-ounce capacity equipped with a plastic screw cap is utilized as the culture flask (fig. 1). The screw cap closure prevents the deterioration of the medium by drying, allowing a supply of bottles prepared for



FIG. 1 — Culture flask with plastic screw.

culture to be kept available indefinitely until needed. A supply of them prepared by affixing a paper label on one edge is placed in each room where patients are to be examined, together with such simple tools as are necessary for taking and implanting specimens. The bottle openings are so small that airborne contamination is almost eliminated, and all implanted specimens may be collected at the end of the day and taken to the laboratory. These bottles cost less when new than the labour charge involved in cleaning an equal number of test tubes to be used again. The laboratory is kept clean

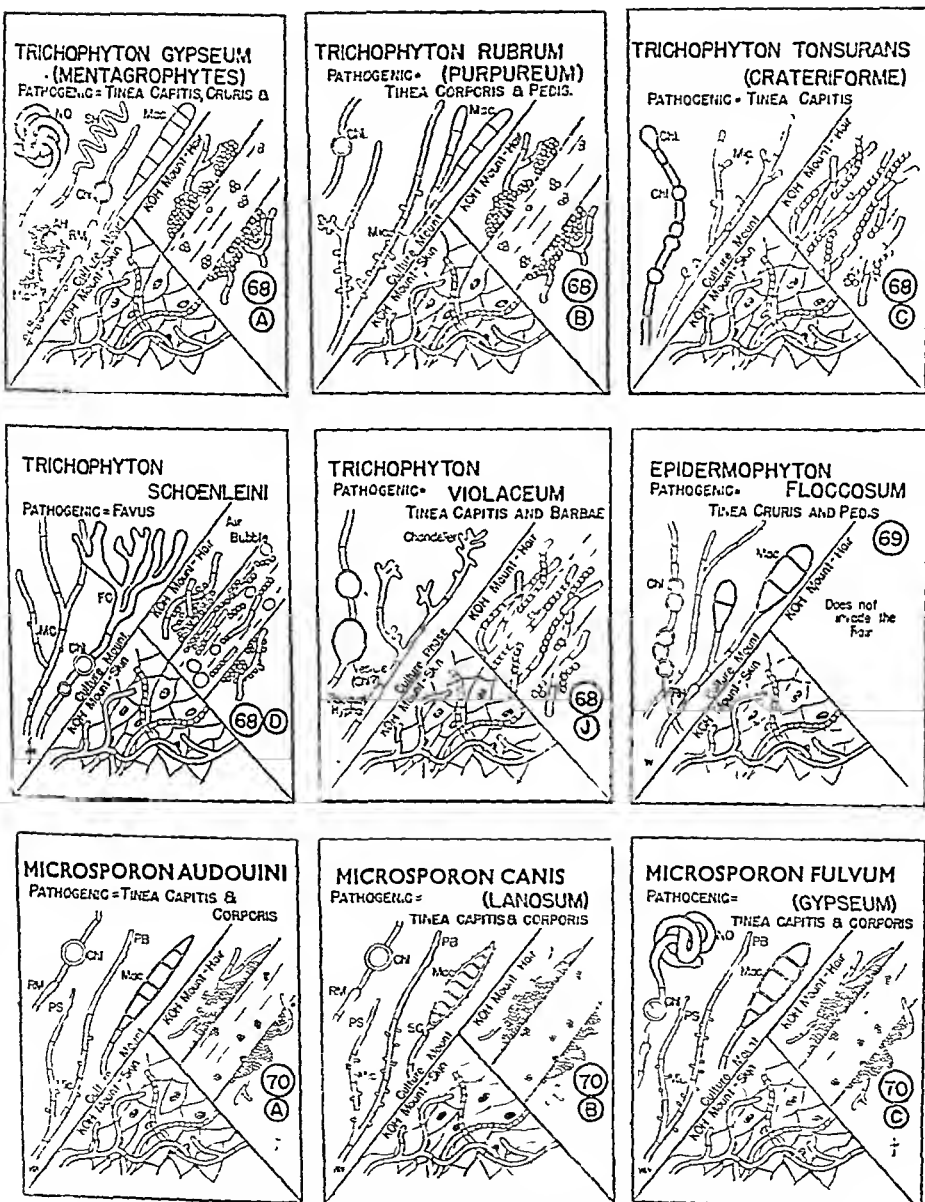


FIG. 2.—MICROSCOPIC FEATURES OF SOME FUNGI RESPONSIBLE FOR SUPERFICIAL MYCOSES
(PLUNKETT AND WILSON)

Chl.=Chlamydo-spore.
Mac.=Macroconidium.
PB=Pectinate Body.

AH=Antler Hypha.
Mic=Microconidium.
PS=Pseudo-spiral.
SH=Spiral Hypha.

FC=Favic Chandelier.
NO=Nodular Organ.
RM=Racquet Mycelium.

additional inoculations should be made deeply into broth which is overlaid with thioglycollate medium. *Blastomyces dermatitidis* is best isolated primarily on glucose agar plates containing blood and held at 37° C. In dealing with cases in which the presence of this organism might be expected this method should be employed concurrently.

The *technique of inoculation* is extremely simple. Tissue fragments need only to be imbedded firmly but superficially in the centre of the agar surface. A moist contact is essential. It is sometimes advantageous to utilize several fragments implanted in different areas; if a single fragment is considered sufficient it should be forced into the agar surface at several different points before it is finally left. By these measures the resulting colony is likely to reach a sufficient size for identification purposes more rapidly. Cultures should be inspected every few days; some fungi are much more easily recognized at one particular stage than at any other.

There are in existence large numbers of different forms of fungi from which less than fifty pathogenic species must be differentiated. Such methods as differential staining, fermentation reactions and other biochemical differences, so useful in identifying bacteria, are of value only in isolated instances in mycology. Most frequently, identification must be made by the observation of the gross and microscopic morphology of the fungus as it grows in culture. The study of the gross appearance of colonies of various fungi would be rendered much easier if an extensive atlas of illustrations in accurately shaded colours could be published. Efforts are being made in several localities towards this end, but financial considerations present a great deal of difficulty. It is still necessary to utilize collections of preserved specimens of actual colonies of fungi for comparison. The use of the small square bottles previously described makes the building of such a teaching collection much more practical than heretofore, since they may easily be hermetically sealed. Simply closing the caps tightly will serve for several months; sealing them with plastic cement will make the specimens last for years.

INTERPRETATION OF RESULTS

The identification of fungi by microscopic study has also been much simplified in recent years. Many workers insufficiently familiar with fungi in general caused confusion in the early literature by publishing incomplete or inaccurate descriptions of organisms and the diseases thought to have been caused by them. The same fungus was described under many different names and classification was rendered difficult. It is now established that rather extensive variations are to be expected in all species of forms of life and that only the larger and more constant differences should be used to delineate separately named groups. Principally in the last decade an extensive and laudable "housecleaning" has taken place in the nomenclature of medical mycology; in some instances literally hundreds of "species"

have been reduced to synonymy. The recent textbook of Conant, Martin, Smith, Baker and Callaway (1944) and that of Lewis and Hopper (1944) will serve the student of medicine admirably in this regard by the reduction of all significant differences in microscopic morphology to a series of easily understood diagrams. We have also been developing an extensive series of such diagrams which is as yet too incomplete for final publication. Such plates when completed, however, have been distributed on several occasions and can be made available to those especially interested. Figures 2 and 3 illustrate some of the fungi involved in the deep and superficial mycoses. The revision of Henrici's "Yeasts, Molds and Actinomycetes" by Skinner, Emmons and Tsuchiya (1947) is valuable because it affords a wider view of mycology in a concise interesting manner.

By using the method described by Huber and Caplin (1947) a collection of slides representing permanently preserved specimens of culture fragments may be assembled for study and reference. The liquid employed combines the preserving and clearing qualities of the lactophenol usually used for preparing culture mounts, with polyvinyl alcohol which causes the specimen to harden within a day or two into a glassy, resistant, permanent plastic. We recommend the addition of 0.3 per cent. of "Porrier's Cotton Blue" dye, since we find that without this the mounting medium is too efficient as a clearing agent and after several months it becomes difficult to discern the fungous elements. One of us (O.A.P.) is at present studying several other dyes in this connexion. If this medium is substituted for the ordinary lactophenol for all microscopic examinations of cultured fungi it is necessary only to place aside until dry those specimens which are found to be sufficiently valuable for addition to the permanent collection; with the growing experience of the operator the collection expands without additional specialized effort.

The identification of fungi in culture is not always simple. It is surprising, however, how quickly a usable degree of proficiency in this regard may be acquired. It is easy to become familiar with the organisms most frequently encountered; at first the more difficult ones may be referred to more experienced workers. Soon, in many areas of the world it will rarely be necessary to send cultures out of the immediate vicinity for identification.

The interpretation of the significance of cultures of material taken from the ano-genital region, ears, nose or mouth presents special difficulties. Fungi capable of pathogenicity are frequently found in these localities in normal individuals or in such circumstances that their causative relation to the disease under study must be seriously questioned. The principal offenders in this regard are species of *Candida* (monilia) and the *Actinomyces-Nocardia* group. The method which has been suggested of cleansing the surface before the specimen is taken will eliminate much of this confusion. Sputum often acquires non-specific fungi during its passage through the mouth; this feature may be eliminated by using material ob-

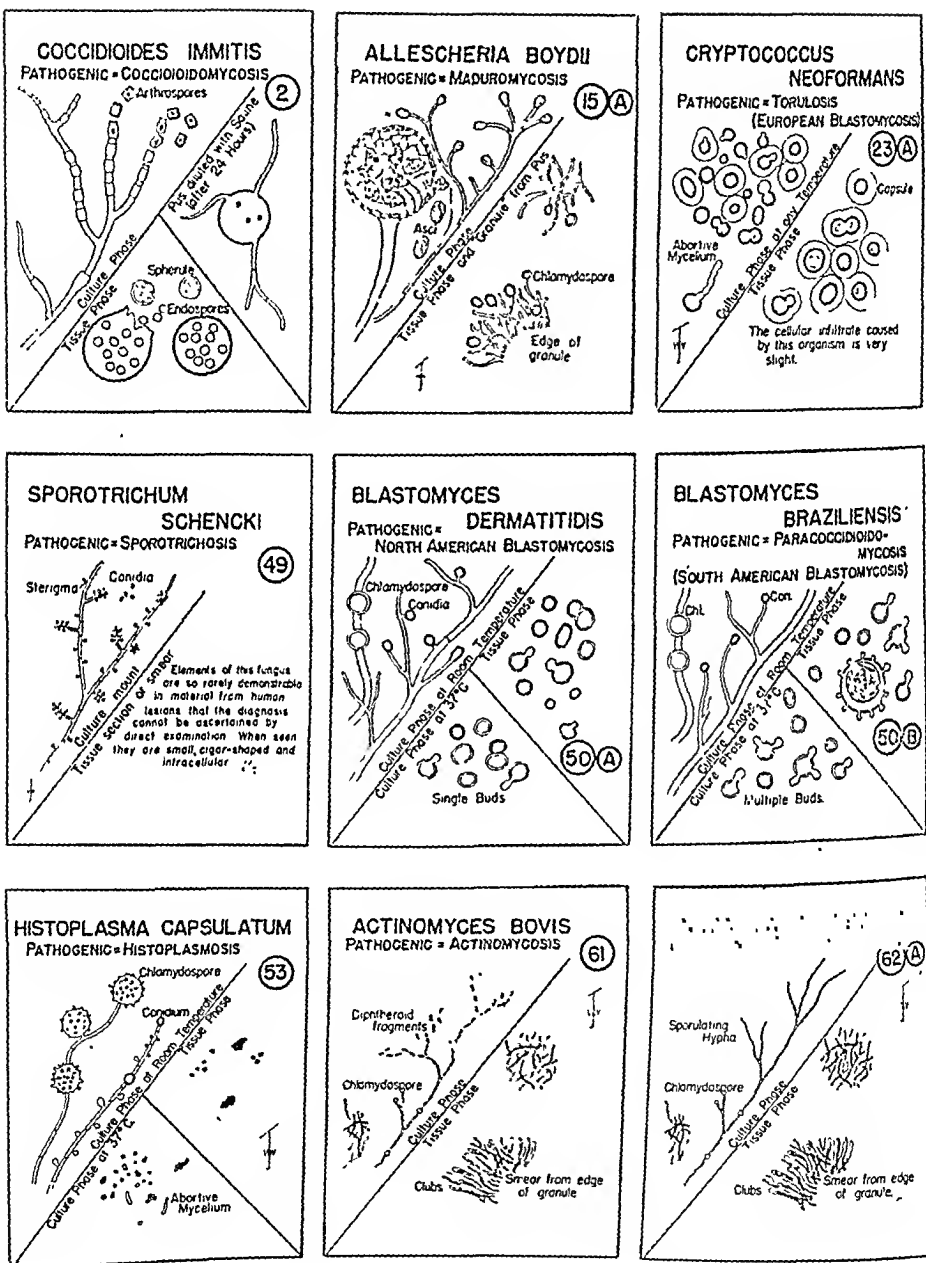


FIG. 3.—MICROSCOPIC FEATURES OF SOME FUNGI RESPONSIBLE FOR DEEP MYCOSES

have been reduced to synonymy. The recent textbook of Conant, Martin, Smith, Baker and Callaway (1944) and that of Lewis and Hopper (1944) will serve the student of medicine admirably in this regard by the reduction of all significant differences in microscopic morphology to a series of easily understood diagrams. We have also been developing an extensive series of such diagrams which is as yet too incomplete for final publication. Such plates when completed, however, have been distributed on several occasions and can be made available to those especially interested. Figures 2 and 3 illustrate some of the fungi involved in the deep and superficial mycoses. The revision of Henrici's "Yeasts, Molds and Actinomycetes" by Skinner, Emmons and Tsuchiya (1947) is valuable because it affords a wider view of mycology in a concise interesting manner.

By using the method described by Huber and Caplin (1947) a collection of slides representing permanently preserved specimens of culture fragments may be assembled for study and reference. The liquid employed combines the preserving and clearing qualities of the lactophenol usually used for preparing culture mounts, with polyvinyl alcohol which causes the specimen to harden within a day or two into a glassy, resistant, permanent plastic. We recommend the addition of 0.3 per cent. of "Porrier's Cotton Blue" dye, since we find that without this the mounting medium is too efficient as a clearing agent and after several months it becomes difficult to discern the fungous elements. One of us (O.A.P.) is at present studying several other dyes in this connexion. If this medium is substituted for the ordinary lactophenol for all microscopic examinations of cultured fungi it is necessary only to place aside until dry those specimens which are found to be sufficiently valuable for addition to the permanent collection; with the growing experience of the operator the collection expands without additional specialized effort.

The identification of fungi in culture is not always simple. It is surprising, however, how quickly a usable degree of proficiency in this regard may be acquired. It is easy to become familiar with the organisms most frequently encountered; at first the more difficult ones may be referred to more experienced workers. Soon, in many areas of the world it will rarely be necessary to send cultures out of the immediate vicinity for identification.

The interpretation of the significance of cultures of material taken from the ano-genital region, ears, nose or mouth presents special difficulties. Fungi capable of pathogenicity are frequently found in these localities in normal individuals or in such circumstances that their causative relation to the disease under study must be seriously questioned. The principal offenders in this regard are species of *Candida* (monilia) and the *Actinomyces-Nocardia* group. The method which has been suggested of cleansing the surface before the specimen is taken will eliminate much of this confusion. Sputum often acquires non-specific fungi during its passage through the mouth; this feature may be eliminated by using material ob-

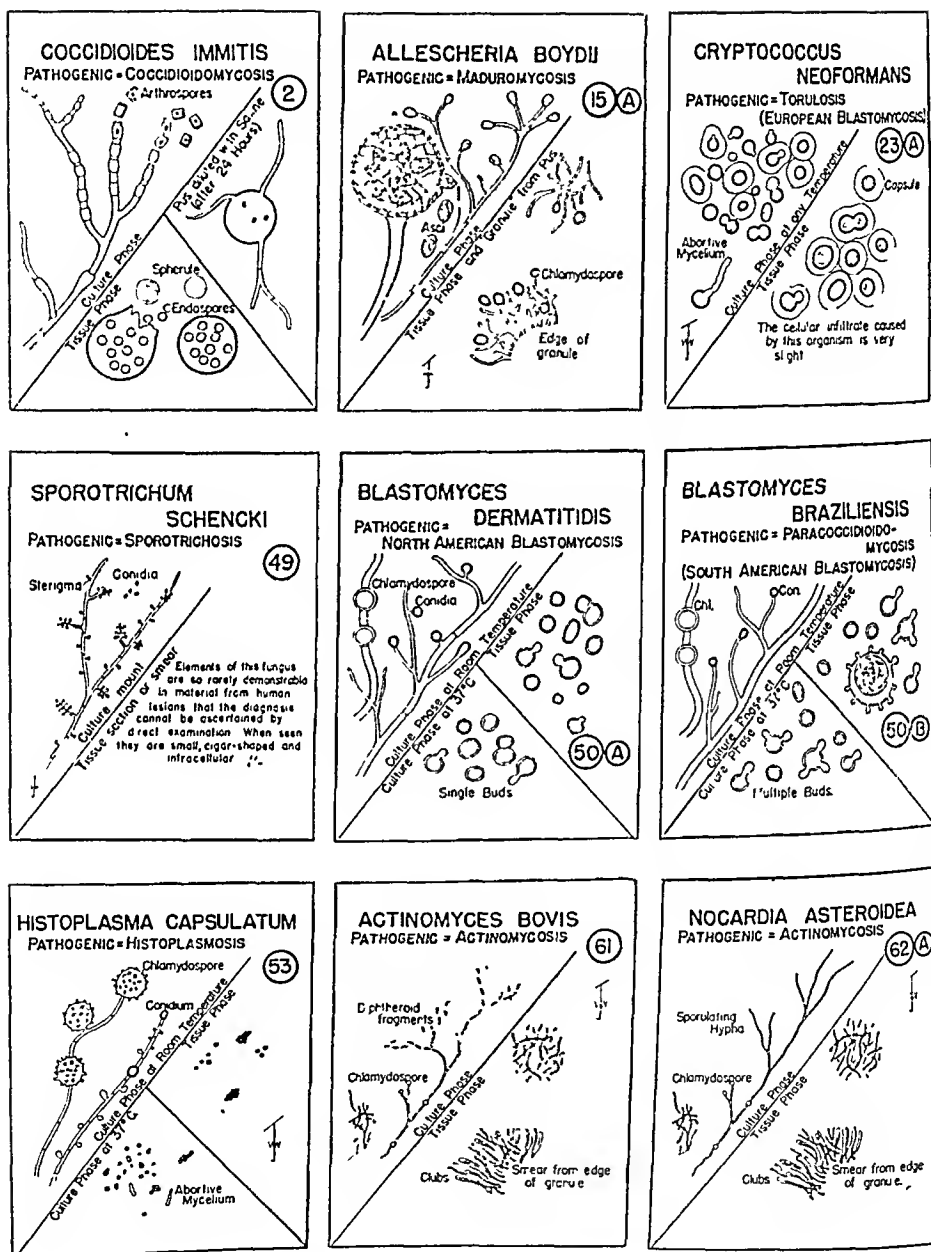


FIG. 3.—MICROSCOPIC FEATURES OF SOME FUNGI RESPONSIBLE FOR DEEP MYCOSES

have been reduced to synonymy. The recent textbook of Conant, Martin, Smith, Baker and Callaway (1944) and that of Lewis and Hopper (1944) will serve the student of medicine admirably in this regard by the reduction of all significant differences in microscopic morphology to a series of easily understood diagrams. We have also been developing an extensive series of such diagrams which is as yet too incomplete for final publication. Such plates when completed, however, have been distributed on several occasions and can be made available to those especially interested. Figures 2 and 3 illustrate some of the fungi involved in the deep and superficial mycoses. The revision of Henrici's "Yeasts, Molds and Actinomycetes" by Skinner, Emmons and Tsuchiya (1947) is valuable because it affords a wider view of mycology in a concise interesting manner.

By using the method described by Huber and Caplin (1947) a collection of slides representing permanently preserved specimens of culture fragments may be assembled for study and reference. The liquid employed combines the preserving and clearing qualities of the lactophenol usually used for preparing culture mounts, with polyvinyl alcohol which causes the specimen to harden within a day or two into a glassy, resistant, permanent plastic. We recommend the addition of 0.3 per cent. of "Porrier's Cotton Blue" dye, since we find that without this the mounting medium is too efficient as a clearing agent and after several months it becomes difficult to discern the fungous elements. One of us (O.A.P.) is at present studying several other dyes in this connexion. If this medium is substituted for the ordinary lactophenol for all microscopic examinations of cultured fungi it is necessary only to place aside until dry those specimens which are found to be sufficiently valuable for addition to the permanent collection; with the growing experience of the operator the collection expands without additional specialized effort.

The identification of fungi in culture is not always simple. It is surprising, however, how quickly a usable degree of proficiency in this regard may be acquired. It is easy to become familiar with the organisms most frequently encountered; at first the more difficult ones may be referred to more experienced workers. Soon, in many areas of the world it will rarely be necessary to send cultures out of the immediate vicinity for identification.

The interpretation of the significance of cultures of material taken from the ano-genital region, ears, nose or mouth presents special difficulties. Fungi capable of pathogenicity are frequently found in these localities in normal individuals or in such circumstances that their causative relation to the disease under study must be seriously questioned. The principal offenders in this regard are species of *Candida* (monilia) and the *Actinomyces-Nocardia* group. The method which has been suggested of cleansing the surface before the specimen is taken will eliminate much of this confusion. Sputum often acquires non-specific fungi during its passage through the mouth; this feature may be eliminated by using material ob-

tained through a bronchoscope. Proof of pathogenic relationship in such circumstances must rest upon repeated examinations yielding positive results consistent with the clinical picture over a period of time during which the pathology cannot be explained on any other basis. In such areas as these, fungi are also commonly encountered which are probably capable of but slight or no pathogenicity; they are simply saprophytes growing in the culture medium furnished by the exudate from some other pathological process. For example, we consider it significant that fungi recovered from cases of so-called "fungus infections of the ear canals" are usually the identical organisms to be found as airborne saprophytes in that part of the world. There is still considerable controversy on this point and future studies must be awaited for reliable answers.

CONCLUSIONS

(1) Many of the factors which have retarded the progress of medical mycology have now been satisfactorily overcome and a usable degree of proficiency in this science may now be attained easily by all those to whom it may be of value.

(2) Medical mycology presents many important and interesting unsolved problems, the answers to which may probably be secured by the expenditure of less effort than in other branches of science.

References

- Conant, N. F., Martin, D. S., Smith, D. T., Baker, R. D., and Callaway, J. L. (1944): "Manual of Clinical Mycology," Philadelphia and London.
- Huber, W. M., and Caplin, S. M. (1947): *Arch. Dermat. Syph., Chicago*, 56, 763.
- Lewis, G. M., and Hopper, M. E. (1944): "An Introduction to Medical Mycology", 2nd edition, Chicago.
- Skinner, C. E., Emmons, C. W., and Tsuchiya, H. M. (1947): "Henrici's Molds, Yeasts and Actinomyces", New York.
- Weidman, F. D., and McMillan, T. M. (1921): *Arch. Dermat. Syph., Chicago*, 4, 451.
- , and Spring, Dorothy (1928): *Ibid.*, 18, 829.
- Wilson, J. W., and Plunkett, O. A. (1949): *Ibid.*, 56, 414.

PSYCHIATRIC REHABILITATION IN HOSPITAL

By J. ERNEST NICOLE, O.B.E., D.P.M.

Medical Superintendent, Winwick Mental Hospital.

THE modern tendency for placing a heavy emphasis on special treatments, especially such physical ones as drug convulsions, electro-shock, insulin coma, modified insulin therapy, prolonged narcosis and leucotomy, may sometimes lead us to underestimate the fact that the main and most widely applicable therapy at our disposal is still rehabilitation in its broadest sense. Many special treatments do not cure so much as make the patient accessible and responsive, thereby paving the way for the application of rehabilitative measures without which treatment would be incomplete.

The various arrangements, amenities and activities that can be included under the heading of rehabilitation are not only numerous but require a high degree of organization, especially when it comes to patients requiring more intensive measures than the average. For instance, if several psychiatrists prescribe different combinations and amounts of various occupations for many patients at a time, there is a real likelihood of creating chaos in the special departments concerned. Those in charge there will find it a wellnigh impossible task to fit in all these different patients so as to ensure the right amount of time and attention being spent on each. It becomes necessary therefore to establish some system whereby there is a *pre-arranged* programme *into which* particular patients can be fitted, rather than attempting to *build up* a programme *round* the many patients' individual requirements as set out, one by one, day by day, by this, that and the other psychiatrist. Hence the need for distinguishing between those activities that can be arranged for the hospital at large, as many patients as possible being encouraged to take part in them, and those occupations that are best carried on in special departments, in small groups, the patients being made to attend at specified times under the supervision of special staff.

A further point is, that in order to help in the selection of cases—especially long-term cases—suitable for intensive rehabilitation, it is necessary to hold, in the wards themselves, “experimental” classes with unimproved patients chosen at random, so that those who show a sufficient response may be passed on to definite programmes. Recent cases, of course, do not offer the same problem, for they are under closer medical observation, and in the early stages of hospitalization intensive rehabilitation is naturally borne well in mind as a likely form of treatment.

Finally, many amenities and facilities have to be provided which, whilst they hardly involve any special activities capable of being programmed,

yet constitute important stimuli in the general rehabilitation and re-socialization of the patient.

SCOPE OF REHABILITATION

ACTIVITIES BEST CARRIED OUT IN SMALL GROUPS, ON A DEFINITE PLANNED TIMETABLE, WITH VARYING PROPORTIONS OF EACH ACTIVITY

(1) *Regular activities in set groups*

Occupational therapy.—This would include occupations such as weaving, rug-work, fancy work, leather work, book-binding, pottery, string work, carpentry, brush making. The work should be planned to provide handicrafts calculated to promote such attitudes as cooperation or competition, routine or initiative, conventionality or originality, whilst some occupations would act as sedatives and others as stimulants.

Physical training.—Here would come all the simpler forms of exercises together with the usual "medicine-ball" games, so as to enlist the interest of the patient, improve his physical state, and especially quicken his reaction time.

Special games.—There should be some sessions devoted to skittle-ball, indoor hockey, basket ball, badminton, table tennis, lawn tennis, bowls, and other games suitable for small groups.

Education.—With due regard to the standard of each particular group, many activities could be included under this heading. Chief among these would be talks on art appreciation, letter writing, local government and citizenship, domestic science, gardening, and other topics of general interest. There would be "quizzes", brains trusts, debates, play reading and so on, as well as competitions.

(2) *Additional in special cases*

Physiotherapy.—Simple physiotherapy, such as massage, special exercises, radiant heat and ultra-violet light, is of help in some cases, particularly as an adjunct to physical training when physical deficiencies are associated with the mental condition (e.g., the vascular deficiency so often found in schizophrenia).

Special classes.—Chief among these would be art classes, music, singing practises, and dancing lessons. These last have the advantage of influencing not only the patient's physical condition but his interest as well, and especially his self-assurance and his facility for social mixing.

Special therapies.—Here, we have speech therapy in cases requiring it, group psychotherapy, psychodrama, and so on.

Utility work.—A start could be made with occupations in a utility department, preparatory to the patient passing on to some full-time activity of a useful nature without special prompting or supervision.

ACTIVITIES OPEN TO LARGE GROUPS OF PATIENTS FROM ALL OVER THE HOSPITAL

Cultural activities.—These would consist of education on a larger scale, in the form of open lectures, debates, special concerts, documentary and instructional films, visits to art galleries, and the like.

Outdoor sport.—A variety should be available and might include football, hockey, rounders, cricket, base-ball and swimming.

Competitive games.—Competition can be encouraged by forming inter-ward leagues at dominoes, whist, table-tennis, billiards, bowls and so on, whilst individual handicaps can also be arranged.

Sedentary games.—In the wards, all the usual sedentary games (draughts, chess, ludo, cards) should be encouraged to the fullest extent possible.

General recreation.—Under this heading would come cinema performances, variety shows, plays, concerts and motor coach outings.

Mixed social functions.—Domino drives, whist drives, mixed bowling, together with dances and parties would be examples, whilst a good mixed Social Club is an absolute necessity if the patient's resocialization is to be pursued adequately.

Full-time useful occupations.—Work in a ward, kitchen, laundry, sewing room, mess rooms, homes, bakehouse, tailors' shop, stores, farm, and gardens provides a means of re-training the patient in independence and in the acceptance of responsibility, as well as maintaining his improvement, strengthening his self-respect and preparing him for re-entry into the outside world.

AMENITIES AND ARRANGEMENTS ON GENERAL LINES

Newspapers.—These should be plentiful, varied and include a fair proportion of illustrated weeklies.

Books.—A good library with sections on special subjects (technical, biography, travel, politics) not only provides recreation but is an indispensable adjunct to the educational side of rehabilitation, often providing a basis for a certain amount of directed reading.

Wireless and radiograms.—There should be individual wireless sets for each ward day-room, with extensions to dormitories occupied during the day. Certain broadcasts (e.g., on politics, current affairs) form a good starting-point for discussion groups. Radiograms are necessary for the Social Club, small dances, talks on musical appreciation, and so on.

Canteen.—A shop where patients can make their own purchases helps them to feel independent and encourages their sense of responsibility.

Tea-room.—The social aspect of rehabilitation depends much upon the presence of a tea-room where patients can go and have tea with their friends of both sexes.

Hairdressing room.—To restore a patient's pride in his appearance, a good hairdressing room is of help; it is indeed a necessity for women, who need permanent waving, resets, shampoos, and the like.

Attractive clothing.—The importance of attractive clothes, hats, and shoes cannot be overestimated, especially where women are concerned.

Medical appliances.—Not only may spectacles, false teeth, surgical shoes and other appliances be required for purely physical reasons, but they acquire considerable psychological importance when their inadequacy or absence undermines the patient's good appearance and self-assurance.

Social work.—In addition to the indispensability of a social worker for obtaining case histories and environmental reports, her presence is very necessary to help the patient in connexion with any personal or family problem which may be distressing him.

Religious help.—This is sometimes required in that many a patient's religious outlook may have been disturbed by his illness, to say nothing of those cases in which a headlong flight into religious preoccupations has occurred as an escape from some other form of mental stress; this proving an occasion for collaboration between the psychiatrist and the priest.

Personal freedom.—The maximum degree of personal liberty consistent with safety is essential in any rehabilitation scheme. This can take the form of parole in the hospital whereby the patient has freedom to go unescorted to the canteen, tea-room, library, hairdressing room and Social Club meetings. Parole can also be extended to include the grounds and even beyond them to neighbouring towns. Again, many patients are fit for "open-door" wards where keys are conspicuous by their absence. Staying up at night without supervision is another privilege that is much valued.

Encouragement and rewards.—To whatever degree useful work may assist a patient's recovery, his efforts in that direction should be accorded due recognition. Whilst his entertainments and social functions are in part a reward for good and

cooperative behaviour, a small payment for work done is advisable in that it is a more tangible form of recompense and helps the patient to achieve a degree of independence and self-esteem. The reward can suitably be given in the form of "tokens" that can be cashed at the canteen in exchange for goods and as free issues of tobacco or sweets.

Outside contacts.—These are very desirable, to prevent the development of a distressing feeling of isolation. Parole beyond the grounds will ensure the possibility of some such contacts, just as leave of absence at the week-end will enable a patient to spend one, two or three days with his relatives. The visiting of the hospital by relatives should be made reasonably easy, the supply of stationery for writing home should be liberal, whilst further contacts with outside friends can be achieved by means of guest nights at Social Club meetings. Also to be encouraged are games against outside teams, visits to local theatres, and so on.

Contented relatives.—Nothing is more conducive to a patient's recovery than the understanding and contentment of the relatives and friends by whom he is visited. To this end, attention must be paid to the adequacy and tone of replies to relatives' letters and inquiries, to facilitating their contacts with the medical staff, and the best means of making them feel they are part of the team ensuring the patient's recovery. Printed information should be available so as to enlist their cooperation and give them a sound understanding of the hospital and its work.

Re-training.—Re-training may sometimes be achieved by means of suitable occupation when the patient is still in hospital, whilst the re-training centres of the Ministry of Labour may be used after discharge to enable a patient to undertake a new kind of employment recommended by the psychiatrist as more psychologically suited to him than his old one.

Resettlement.—The fitting of the patient into employment after discharge often requires the previous help of the Resettlement Officers of the Ministry of Labour, who can also assist in the sometimes difficult question of finding the patient living accommodation at or near the place of work.

After-care.—Liaison is required between the psychiatric social worker in the hospital and outside social workers to ensure adequate after-care when necessary. Information concerning the patient, his illness, his past treatment, his condition on discharge and any suggestions for after-care should be sent not only to the Medical Officer of the Local Health Authority but also to the patient's own doctor, whilst arrangements might have to be made for future attendances at psychiatric clinics.

ORGANIZATION

This must vary considerably from hospital to hospital, and the scheme outlined below, based on the methods that have been in use at Winwick for some years, in no wise pretends to be ideal or, indeed, anything more than one attempt at solving some of the problems of organization in a hospital of 2,200 beds.

Intensive groups.—Twelve groups have been established for twenty to thirty patients each, with varying combinations of activities undertaken on a sessional basis, each session lasting for an hour and a half and occupying half the morning or afternoon.

In the first group, the afternoons only are occupied, because it is intended for patients who are on special treatments in the mornings; in the middle groups the sessions are more numerous, and in the higher ones a degree of useful work is introduced; in these, the sessions for day entertainments are less, the patients being probably fit to attend evening performances. Each

group having certain periods free, it is easy to fit in (by individual prescription) such additional activities as physiotherapy, group therapy or dancing lessons. Moreover, it is good for the patients to have these opportunities for adjusting themselves to ward conditions and playing sedentary games, to have such sessions when they must themselves decide what they will do, and to be under the renewed observation of the nursing and medical staff in the ward. The psychiatrists have only to prescribe the group number that seems to fit the patient best and thereafter the occupation of that patient's time, day by day, is regulated by the timetable set up for all the groups. The rehabilitation officers (occupational therapists, physical training instructors and instructresses, education officers, librarian) meet once a week to discuss their cases, after which the education officers contact the psychiatrists to report and also to go over possible regroupings due to congestion in one group and vacancies in another, as well as promotions from group to group, the ultimate aim being to pass patients out of the groups altogether on to full-time occupation in departments or wards.

TABLE 1

INTENSIVE REHABILITATION

WEEKLY NUMBER OF SESSIONS ALLOCATED TO OCCUPATIONAL THERAPY (O.T.), PHYSICAL TRAINING (P.T.), SPECIAL GAMES (G.), EDUCATION (E.), UTILITY WORK (U.) AND ENTERTAINMENTS (ENT.) FOR THE GROUPS AND FOR WARD CLASSES

Activity	Men's Groups						Women's Groups						In the Wards	Total
	I	II	III	IV	V	VI	I	II	III	IV	V	VI		
O.T. ..	3	6	5	4	3	—	3	7	6	4	3	—	} 16 32 22 —	70
P.T. ..	3	—	5	4	2	1	1	—	5	4	3	1		73
G. ..	—	—	—	1	3	3	—	—	—	1	3	3		34
E. ..	—	—	—	2	2	2	—	—	—	2	2	2		—
ENT. ..	4	4	4	4	2	2	4	4	4	4	2	2	—	—
U. ..	—	—	—	—	6	10	—	—	—	—	6	10	—	—
Total	10	10	14	15	18	18	8	11	15	15	19	18	70	177

Experimental classes.—Classes in occupational therapy, in physical training and/or games, and in education are held once or twice weekly in each of a number of selected wards. Certain patients will thereby be found sufficiently responsive to justify their being recommended for inclusion in the intensive groups, whilst others will at least become less idle and also more responsive, easier to manage and consequently less likely to deteriorate further. The weekly number of sessions for different activities allocated to each of the special groups and to experimental ward classes will be found set out in table 1. As an example of one day's work, the timetable for Mondays is given in table 2.

Large-scale activities.—Here it is merely a matter of arranging a weekly

programme, many of the activities being at night so as to allow those patients who are on full-time occupations during the day to get most of their

TABLE 2
INTENSIVE REHABILITATION
EXAMPLE OF GROUP AND WARD TIMETABLE FOR ONE DAY (MONDAYS)

Times of sessions	MEN							MIXED	WOMEN							
	GROUPS						Ward sessions		Open to all	Ward sessions	GROUPS					
	I	II	III	IV	V	VI					I	II	III	IV	V	VI
9 to 10.30	T.	O.T.	O.T.	P.T.	U.	U.	P.T.	—	P.T.	T.	O.T.	P.T.	—	E.	U.	
10.30 to 12	T.	—	P.T.	O.T.	U.	U.	E.	—	O.T.	T.	—	O.T.	E.	G.	U.	
1.30 to 3	O.T.	—	—	G.	O.T.	E.	P.T.	Inter-ward Bowling League	E., P.T.	—	O.T.	—	P.T.	O.T.	—	
3 to 4.30	P.T.	—	—	E.	G.	—	O.T.		P.T.	O.T.	—	—	O.T.	—	P.T.	
6 to 7	—	—	—	—	—	—	E.	Social Club Meeting	E.	—	—	—	—	—	—	
7 to 9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	

T. .. Special Treatments.
O.T. .. Occupational Therapy.
G. .. Games.

P.T. .. Physical Training.
E. .. Education.
U. .. Utility Occupation.

recreations after normal working hours, although needless to say no patient would be debarred from attending any function which is held exclusively during the day. The general plan on which the weekly programme is built is given in table 3.

GENERAL ARRANGEMENTS

The list previously given is largely self-explanatory and only a few additional comments need be made.

The Social Club membership is open to all patients on parole but is limited in number to a hundred. The club is run by the patients themselves and no staff is at any time in charge of them or even present at the meetings, except that psychiatrists and rehabilitation officers attend from time to time, unofficially and merely to give such assistance as may be desirable and acceptable. The club activities include talks, discussions, lectures by visitors, card games, music, competitions; one night a week is kept for sedentary occupations as above, whilst the other weekly meeting is reserved for dancing and for such games as skittle ball, badminton, basket ball and table-tennis in winter, and bowls, golf, tennis and rounders in summer. Once a month the club has a guest night at which relatives and ex-patients may attend by invitation, and these are often occasions for having matches of various games against local teams and Youth Clubs. Patients submit their own applications for membership, supported by the psychiatrist's approval, after which the patient may be accepted (and may subsequently be expelled!) at the discretion of the Club Committee. In order that vacancies

should always be available to recent and recovering patients, there is a system whereby the older and less useful members retire in rotation.

TABLE 3
LARGE-SCALE REHABILITATION

MONDAYS	..	Every Monday	..	Afternoon: Men's inter-ward domino league (winter) or bowling league (summer)
		" "	..	Night: Mixed social club games meeting in hall (winter) or outdoors (summer)
TUESDAYS	..	One Tuesday in four	..	Afternoon: Mixed whist drive
		" " " "	..	" Mixed domino drive
		" " " "	..	" Mixed dance for less good patients (not in four summer months)
		" " " "	..	Night: Mixed dance for good patients (not in four summer months)
		" " " "	..	Concert, play or stage show
WEDNESDAYS	..	Two Tuesdays in four	..	Evening: Mixed singing practice
		Every Wednesday	..	Afternoon: General visiting by relatives
		" "	..	Evening: Mixed practice dance for special class (winter only)
		" "	..	" Mixed bowling (summer only)
		One Wednesday in four	..	Night: Open educational session, instructional films, etc.
THURSDAYS	..	Every Thursday	..	Afternoon: Football or cricket for men (largely rehabilitation groups)
		" "	..	" Hockey or rounders for women (largely rehabilitation groups)
		" "	..	" Mixed ballroom dancing class (winter only)
		" "	..	" Cinema show for less good patients
FRIDAYS	..	Every Friday	..	Night: Cinema show for good patients
		" "	..	Afternoon: Men's inter-ward billiard league (winter) or bowling league (summer)
SATURDAYS	..	Every Saturday	..	Night: Mixed social club sedentary meeting
		" "	..	Afternoon: General visiting by relatives
		" "	..	" Staff cricket match or outside team football match
		" "	..	" Individual knock-out bowling (summer only)
SUNDAYS	..	Every Sunday	..	Morning: Roman Catholic service
		" "	..	" Church of England service
		" "	..	Afternoon: Nonconformist service
		" "	..	" Special visiting by relatives

ADDITIONAL: Cricket and bowling matches "away" against other hospitals, motor coach outings (two per week in summer), sports day, ward and other parties

It is calculated that *parole* "in the hospital" can be granted to 15 to 20 per cent. of the *ambulant* population, whilst "grounds" parole and "outside" parole would account for another 8 to 15 per cent. each, giving a total of 30 to 50 per cent., according to the nature of the cases under treatment and the proportion of difficult chronic patients the hospital has to carry. Cooperative patients should get parole "in the hospital" within a matter of days after admission, and to this end there are two admission wards on each side, the one on the "open-door" principle for well-behaved patients, and the other for disturbed cases, so that good patients (whether certified or voluntary) can immediately or very shortly after admission be placed in a ward from which they have unlimited access to all parts of the hospital. At present the total number of patients housed in open-door wards is 680, whilst the number on varying degrees of parole is rather more.

The Library has usually about 18,000 books, of which some 2000 are on the ward shelves. Ward books are changed once monthly and the Librarian and Assistant Librarian (with the help of several patients) supervise these exchanges and also take round trolleys of special books for non-parole patients to choose their own. The Library has special rooms for technical

programme, many of the activities being at night so as to allow those patients who are on full-time occupations during the day to get most of their

TABLE 2
INTENSIVE REHABILITATION
EXAMPLE OF GROUP AND WARD TIMETABLE FOR ONE DAY (MONDAYS)

Times of sessions	MEN						Mixed	WOMEN								
	GROUPS							Ward sessions	Open to all	Ward sessions	GROUPS					
	I	II	III	IV	V	VI					1	II	III	IV	V	VI
9 to 10 30	T	O T	O T	P T	U	U	P T.	—	P T	T	O T	P T	—	E	U	
10 30 to 12	T	—	P T	O T	U	U	E	—	O T	T	—	O T	E	G	U	
1 30 to 3	O T	—	—	G	O T.	L	P T	Inter-ward Bowling League	E, P T	—	O T	—	P T	O T	—	
3 to 4 30	P T	—	—	E	G	—	O T		P T	O T	—	—	O T	—	P T	—
6 to 7	—	—	—	—	—	—	E	Social Club	E	—	—	—	—	—	—	
7 to 9	—	—	—	—	—	—	—	Meeting	—	—	—	—	—	—	—	

T . Special Treatments
O T Occupational Therapy
G Games

P T Physical Training
E Education
U Utility Occupation

recreations after normal working hours, although needless to say no patient would be debarred from attending any function which is held exclusively during the day. The general plan on which the weekly programme is built is given in table 3.

GENERAL ARRANGEMENTS

The list previously given is largely self-explanatory and only a few additional comments need be made.

The Social Club membership is open to all patients on parole but is limited in number to a hundred. The club is run by the patients themselves and no staff is at any time in charge of them or even present at the meetings, except that psychiatrists and rehabilitation officers attend from time to time, unofficially and merely to give such assistance as may be desirable and acceptable. The club activities include talks, discussions, lectures by visitors, card games, music, competitions; one night a week is kept for sedentary occupations as above, whilst the other weekly meeting is reserved for dancing and for such games as skittle ball, badminton, basket ball and table-tennis in winter, and bowls, golf, tennis and rounders in summer. Once a month the club has a guest night at which relatives and ex-patients may attend by invitation, and these are often occasions for having matches of various games against local teams and Youth Clubs. Patients submit their own applications for membership, supported by the psychiatrist's approval, after which the patient may be accepted (and may subsequently be expelled¹) at the discretion of the Club Committee. In order that vacancies

THE PRESENT POSITION OF SURGERY IN THE TREATMENT OF PARKINSONISM

By LESLIE C. OLIVER, F.R.C.S.

Neurosurgeon, West End Hospital for Nervous Diseases, and Royal Northern Hospital, London; Surgeon in charge, Neurosurgical Centre, Oldchurch Hospital, Romford.

DURING the past year the lay press has given considerable publicity to this subject, with the result that medical practitioners have been inundated with inquiries from patients with Parkinson's disease or the allied disorder of postencephalitic Parkinsonism. Therefore it is opportune that an account should be given of what can and what cannot be accomplished by surgery in the treatment of Parkinsonism. Let it be stated at once that there is no absolute cure for the disease. However, in carefully selected cases, operative treatment offers a reasonable prospect of worth-while relief from tremor.

CASES SUITABLE FOR SURGERY

The fully developed picture of Parkinsonism is well known. The face is expressionless, the limbs are in a constant state of tremor, the patient shuffles along in a flexed attitude with a tendency to break into a run forward (propulsion) or sometimes backward (retropulsion). Above all, there is a gross degree of helplessness out of all proportion to any loss of muscular power that may be observed.

The fully developed classical case of Parkinsonism has nothing to gain from surgery, with the exception that excessive salivation can be substantially reduced by means of avulsion of the auriculo-temporal nerves which supply the secreto-motor fibres to the parotid glands.

There are, however, many patients in whom tremor is practically the only manifestation, and in the more fortunate ones it is unilateral. It is these cases that it is possible to help by surgical means. The operations to be described give the best results in patients with one-sided tremor. It must be clearly understood that the operations are designed for the relief of tremor when this symptom is of gross degree and other effects of the disease are negligible. If there is tangible muscular weakness, marked slowing and awkwardness of movement of all the limbs and emotional changes, operative treatment will only make matters worse.

SURGICAL PROCEDURES

In 1903, Rothmann showed that division of the lateral pyramidal tracts in monkeys gave rise to little or no apparent disability. Combining this evidence with the fact that a patient suffering from Parkinson's disease is

subjects as well as a reading and other rooms attached which are also used by the Social Club at night. One of these is reserved during the day for educational classes. Also attached to the Library premises are offices for the Chaplain and Librarian, for the Education Officers and for the Psychiatric Social Worker.

The hairdressing room for ladies is not on an elaborate scale but a good full-time hairdresser with the help of a patient easily deals in the course of a month with at least 25 to 30 "perms", over 100 resets and shampoos, and some 300 to 350 cuts and trims.

The very necessary *education of relatives* and of the public generally in matters psychiatric is attempted in two ways. The relatives of every newly admitted patient receive a long printed letter explaining the light in which a mental illness should be regarded, the necessity for early and adequate treatment, the amenities available to patients, the attitude the relatives should adopt when visiting, the need for their help and cooperation, the prospects of recovery and the fact that some 80 per cent. of patients go home again, the risks of too early a discharge, and so on. For other laymen, especially those for whom their official or public work make some understanding of psychiatry if not essential at least desirable, a booklet is published by the hospital giving in simple language the main facts about the nature of mental illness, its principal forms, its many causes, the multiple approaches to treatment, together with procedures for hospitalization and discharge. All this leads to a good understanding with relatives and others, and may indeed have contributed to the fact that the proportion of voluntary patients in direct admissions has been found to rise from about 25 per cent. to 70 per cent. in five years.

CONCLUSION

It should be emphasized that the general scheme of rehabilitation must be under the control of *one* psychiatrist—in consultation with his colleagues, of course—whilst the question of resettlement and after-care on discharge should also be one person's concern.

Although nothing in the foregoing can be looked upon as new or original, it may be that the bringing together in a few remarks of all that can be termed "rehabilitation" may assist in surveying the whole field more completely and from a more unified point of view than is sometimes done.

The results of the above operation throw doubt on the previously accepted views regarding the importance of the crossed pyramidal (cerebrospinal) tracts. These tracts were thought to convey practically all the nervous impulses concerned with power and movement. Interruption of these fibres was assumed to give rise to complete paralysis below the level of the lesion. It is now evident, however, that the pyramidal fibres in the anterior columns (anterior cerebrospinal tracts) are of great functional significance. In two instances only was there a Horner's syndrome on the side of the cordotomy, lasting for a few days only. The division of the posterior spino-cerebellar tract seemed to be without effect. Even after bilateral cordotomy there was no interference with the function of the diaphragm, and except in one case, in which there was some enlargement of the prostate, retention of urine occurred for a few days only.

CEREBRAL AND SPINAL OPERATIONS COMPARED

Cerebral Operation	Spinal Operation
Complete relief from tremor in affected arm. Any tremor in leg unaffected.	Some tremor remains in arm. Tremor completely relieved in leg.
Permanent paralysis of arm after operation.	Slight or no permanent paralysis.
Suitable for unilateral cases only.	Mostly suitable for unilateral cases and a few bilateral ones.
Risk to speech zone on left side.	No risk to speech.
Risk of epilepsy following operation.	No risk of epilepsy.

CONCLUSION

Let it be stressed again that in most patients suffering from Parkinsonism, gross disability is the outstanding feature and the tremor is a secondary consideration. If operation is performed for this, the classical syndrome, the patients will be made worse and surgery's modest contribution towards the treatment of the disease will be discredited.

References

- Bucy, P. C. (1949): Personal communication.
 —, and Case, T. J. (1939): *Arch. Neurol. Psychiat.*, 41, 721.
 Oliver, L. C. (1949): *Lancet*, i, 910.
 Putnam, T. J. (1940): *Arch. Neurol. Psychiat.*, 44, 950.
 Rothmann, M. (1903): *Z. klin. Med.*, 48, 10.

relieved from tremor on the contralateral side following a cerebral apoplexy, Putnam (1940) tried the effect of division of the lateral pyramidal tract in cases of unilateral Parkinsonian tremor. He was able to report encouraging results in seven cases. Again in unilateral cases, Bucy and Case (1939) succeeded in abolishing tremor by excising cerebral cortex immediately in front of the fissure of Rolando, but at the expense of complete paralysis of the affected limb. During the past two years I have been performing a modified Putnam cordotomy and have extended its application to bilateral cases. This operation offers substantial, but not complete, relief from tremor without permanent paralysis.

Regional excision of cerebral cortex.—Bucy (1949) continues to perform cerebral operations for unilateral cases in which violent tremor affects one arm. He maintains that the operation is indicated if both the patient and the surgeon have no doubt that a paralysed arm is better than a disabled and tremulous one.

The pre-motor area representing the upper extremity is located by electrical stimulation, and it is then excised to the full depth of the grey matter. The surgeon takes great care not to injure the main cortical vessels in the vicinity by using the Horsley technique of sub-pial dissection.

Cordotomy.—Radical division of the lateral pyramidal tract (Oliver, 1949) is also indicated when tremor is without doubt the outstanding feature and other effects of the disease are minimal. Tremor must be the symptom for which the patient seeks relief.

The spinal cord is exposed by the removal of the laminæ of the second and third cervical vertebræ, followed by a longitudinal incision in the dural and arachnoid membranes. A No. 15 blade is held in a Spencer-Wells forceps so that 5 mm. of the blade project beyond the beak. With the cutting edge directed anteriorly, the surgeon thrusts the point of the knife into the cord at the site of entry of a convenient posterior nerve rootlet. This transverse cut is made at the level of the second cervical spinal segment. The blade enters the cord to a depth of 5 mm. and is then made to sweep laterally to complete the cordotomy. After operation there is a complete hemiplegia from which, in the majority of cases, it does not take more than a few weeks to recover.

RESULTS

An analysis of the first series, comprising forty-eight operations, showed that tremor had been reduced to a negligible degree in 24 cases (50 per cent.) and the usefulness of the arm was substantially improved in 21 instances (44 per cent.). The second series will be reported later, but it is already evident that results are greatly improving as more experience is gained in the selection of cases. The operation is indicated in only a small proportion of patients affected with bilateral tremor. Again, the other symptoms of the disease must be of slight degree, and the tremor should be so violent that life is intolerable. Two operations will be necessary, separated by an interval of several months. A period of rehabilitation is essential after operation, especially in bilateral cases.

although English equivalents are also given. It is difficult to understand why part V (surgical dressings) was not included among the exceptions. Whilst there may be much to be said from the international point of view for the retention of official Latin names, the results of their retention for surgical dressings are scarcely impressive. How many practitioners to-day will be able to recognize "*carbasus absorbens tænia*", "*curatio normalis*", "*emplastrum elasticum pro curationibus*", "*gossypium absorbens*", "*ligamentum crispî*", "*sindon oleata*", "*stupa*", and "*tela barbasi et gossypii*"? It would require the combined skill of the editorial board of *Punch* to do justice to such a selection, and even they would find it difficult to give the English equivalents, which are: absorbent ribbon gauze, standard dressing, elastic plaster for dressings, absorbent cotton-wool, crêpe bandage, oiled cambric, tow, and gauze and cotton tissue. Surely, it would have been more in accordance with modern thought, and not in the least derogatory to the traditions of the past, to have included surgical dressings in the same category as surgical ligatures and sutures.

A wholly commendable feature is the giving of doses in both the metric and the imperial systems, but in the section of the formulary devoted to mixtures it is difficult to understand why the metric formula gives the total amount to be prescribed, whereas the imperial formula merely gives the constituents of one dose. This would appear to be making things unnecessarily difficult, a particularly unfortunate step at the present moment when such active steps are being taken (and rightly so) to persuade practitioners to use the metric rather than the imperial system.

NEW FEATURES

In view of the care which is essential in the "censoring" of new drugs before allowing them to be included in a publication of this importance, the *Codex* is amazingly up to date. For instance, there are monographs on folic acid, dimethyl phthalate, dimercaprol (B.A.L.), proguanil hydrochloride (paludrine), cyclobarbitone, methyl thiouracil, sodium alginate, lachesine, and tubocurarine. Other new monographs include those on penicillin, the synthetic œstrogens, proteolysed liver, oxophenarsine, sulphamerazine, and rauwolfia. An important feature of all the monographs, from the practitioner's point of view, is that they include short notes on action and uses. On the whole these are of a high standard of accuracy and discrimination, and particularly outstanding in this connexion is that on penicillin. The paragraph on the oral use of penicillin, for example, is an admirably sound summary of the present status of this mode of administration of the antibiotic. That the old is not being given up simply because of new arrivals is well exemplified in the monograph on strophanthin-K, which will help to rectify the modern tendency to give up the use of this excellent preparation in favour of one of the newer preparations of digitalis. To criticize simply because monographs are not completely up to date is scarcely justified, but it is a pity that the relative value of the three synthetic œstrogens, stil-

THE BRITISH PHARMACEUTICAL CODEX 1949

By WILLIAM A. R. THOMSON, M.D.

It is difficult for the modern generation of practitioners and pharmacists to realize that it is just over forty years since the *British Pharmaceutical Codex* was first published (1907). In fact, if not in law, it is now looked upon as being in the same category as the *British Pharmacopæia*, and British medicine and pharmacy without its "B.P.C." is like "Hamlet" without the Prince of Denmark. Subsequent codices were published in 1911, 1923 and 1934, and a study of these provides an interesting commentary on the progress of therapeutics during the first three decades of the century. One of the major changes was that the *Codex* tended to become more of a complement to the *British Pharmacopæia*, providing the practitioner and the pharmacist with a guide to the composition of preparations widely used in medicine but not included in the *British Pharmacopæia*.

The intervention of the 1939-45 war postponed publication of a new *Codex* long beyond the usual interval, but this interregnum was covered by a series of seven Supplements. The combination of this delay and the concomitant phenomenal advances in the field of therapeutics has not only meant that the work of revision has taken four years but that the changes between the new *Codex* and its 1934 predecessor are greater than those between any two preceding issues. That the task has been ably accomplished goes without saying, and too much praise cannot be given to the Revision Committee for the skill and care with which they have prepared the 1949 *Codex* which is now available.*

CONTENTS

The general arrangement of the *Codex* is too well known to require elaboration here. As usual, the greater part of the book is devoted to general monographs. For the purpose of the new *Codex* the monographs on antisera, vaccines and related substances have been separated from the general monographs, and constitute part II. Part III is an entirely new feature and is devoted to preparations of human blood. Parts IV and V deal with surgical ligatures and sutures, and surgical dressings, respectively, whilst part VI consists of an admirable series of formulæ. The volume concludes with a valuable series of appendices covering such important features as determination of vitamins, examination of surgical dressings, sterilization, and so forth.

In all sections, except parts III and IV, latinized names are given priority,

* *The British Pharmaceutical Codex, 1949.* Published by Direction of the Council of the Pharmaceutical Society of Great Britain. London: The Pharmaceutical Press. Pp. xxv and 1562. Price 63s.

reasons why a *Codex* published in 1949 should contain a detailed formula of compound syrup of glycerophosphates and pepsin with its eighteen constituents. Incidentally, a 10-ounce bottle contains 25 grains of caffeine and $7/8$ of a grain of strychnine, and the recommended dose is 60 to 120 minims. Even compound syrup of cocillana is somewhat complicated for these days, with its eleven constituents, but it is a pleasing concoction:—

	Metric	Imperial
Liquid extract of cocillana	16.7 ml.	80 minims
Liquid extract of euphorbia	41.7 ml.	200 minims
Liquid extract of senega	4.2 ml.	20 minims
Liquid extract of squill	4.2 ml.	20 minims
Potassium antimonyltartrate	0.14 g.	$5/8$ grain
Codeine phosphate	2.29 g.	10 grains
Menthol	0.18 g.	$5/6$ grain
Spirit of chloroform	41.7 ml.	200 minims
Water	62.5 ml.	300 minims
Glycerin	166.7 ml.	320 minims
Syrup	to 1000.0 ml.	to 10 fl. oz.

Dose: 2 to 4 ml. (30 to 60 minims).

Space does not permit of anything like a full review of the contents of this section, and it need only be added that it is as reliable as it is comprehensive.

THE CODEX AND THE NATIONAL HEALTH SERVICE

Of the value of the *Codex* there is no question. What is of importance, however, at the present moment, is to ensure that all the careful expert work which is put into its compilation should be put to the greatest possible use by the medical profession. In its present familiar guise it would be of the greatest value to practitioners, but there are few to-day who can afford three guineas, and there is some information in it which is not of outstanding use to medical practitioners. Neither is it likely that the Ministry of Health would be prepared to issue it free, or even at a reduced price, to all practitioners. In view of the probable developments under the National Health Service, and of the need for some guide on the increasingly difficult problem of prescribing, the time would appear to have come to give serious consideration to the possibility of bringing out a modified *Codex* which would be issued free, or at cost price, to every medical practitioner in the country. It is generally agreed that the *National Formulary* 1949 is too small to be of much value. The *Codex* is too large. Would it not be possible to bring out a book intermediate in size, which would provide the practitioner with a comprehensive and reliable guide to practical prescribing? Obviously, if such a project were undertaken the present Codex Revision Committee of the Pharmaceutical Society would need to include medical representatives, but the Joint Formulary Committee, which was responsible for the *National Formulary* 1949, provides an admirable precedent for the authoritative guidance which is clearly required if prescribing under the National Health Service is to remain reasonably free from central control and yet be immune from over-prescribing or too expensive prescribing.

bæstrol, dienæstrol, and hexæstrol, are not more accurately assessed. An anomaly, which is also probably unavoidable, is that an injection of a water-soluble vitamin K analogue is, correctly, given as the antidote to overdosage with dicoumarol, but no such analogue is included in the *Codex*. Incidentally, it is somewhat unfortunate that the only antidote to overdosage with heparin that is mentioned is a transfusion of human whole blood. No reference is made to protamine sulphate in this connexion.

The new section on preparations of human blood is a notable addition to the *Codex*. The preparations dealt with are: whole human blood, concentrated human red blood corpuscles, liquid human plasma, dried human plasma, liquid human serum, dried human serum, human fibrinogen, human fibrin foam, and human thrombin. The mere fact that such a section should be included in this edition of the *Codex*, and that it is so thorough and up to date, is a striking commentary on the rapid and sustained advances that have been made in our knowledge of blood transfusion since the outbreak of war in 1939. The section on surgical ligatures and sutures is disappointingly brief, dealing only with surgical catgut, sterile and non-sterile. Surely an unnecessarily small offspring for a special subcommittee of fifteen members, three of whom are among the leading surgeons in this country.

SOME FORMULÆ

The Formulary has undergone thorough revision, and is now a most useful aid to the busy practitioner. Throughout this section standards with tolerances and assay processes have been included, wherever practicable. In spite of revision, much of the old has been retained, and well-proved friends such as Chelsea Pensioner, Andrew Clark's liver pills, Guy's pills, and Whitfield's ointment are still retained. The list of mixtures is particularly interesting; it contains 78 formulæ, twenty-five of which are for children. Of those which are not included in the *National Formulary* 1949, the following may be quoted as useful examples:—

Mixture of Bismuth:—

Bismuth carbonate	45.7 g.
Sodium bicarbonate	45.7 g.
Light magnesium carbonate	45.7 g.
Peppermint water.....	to 1000.0 ml.

Dose: 15 to 30 ml.

Acid mixture of gentian and nux vomica:—

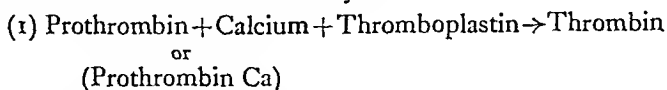
Dilute hydrochloric acid	41.7 ml.
Concentrated compound infusion of gentian	125.0 ml.
Tincture of nux vomica	41.7 ml.
Chloroform water.....	to 1000.0 ml.

Dose: 15 to 30 ml.

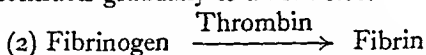
Syrups, one of the few surviving reminders of the days of elegant prescribing, and noticeable by their absence from the *National Formulary* 1949, are well represented. The thirty-two contained in the *Codex* include such nostalgic names as syrup of orange-flower, syrup of poppy, and syrup of black currant. Much as one may reverence the past, it is difficult to find

the addition of suitable coagulant tissue extracts, or of protein substances such as trypsin or snake venoms.

Whilst many of the details of blood coagulation are not clear, the process depends essentially upon at least two main reactions involving prothrombin—calcium and fibrinogen in the plasma and thromboplastin from the platelets and damaged tissues. It is not now believed that heparin plays any significant part. Now this scheme postulates that thromboplastin, liberated from disintegrating platelets or tissue cells when the vessel walls are damaged, initiates the reaction whereby prothrombin is converted to thrombin in the presence of calcium. This latter is present in the plasma, but some believe that prothrombin itself is combined with calcium. Thromboplastin is thought by many to act as a catalyst, but there is some evidence that it acts stoichiometrically:—



When sufficient thrombin has been formed the next main reaction is a catalytic one, in which fibrinogen already present in plasma is converted probably through a loose fibrinogen-thrombin complex to insoluble fibrin, which can be seen under the microscope to be precipitated as long needles in the gel, which contracts gradually to a firm clot:—



The thrombin being an enzyme remains unchanged after this reaction, and so a very small amount is capable of converting a very large amount of fibrinogen, although much of it is absorbed or enclosed within the clot. There are other side-reactions occurring simultaneously but they do not concern us here, e.g. inactivation of prothrombin by the excess thrombin, effects of antithrombin, removal of thrombin by combination with possibly serum albumin. It is obvious that failure of this mechanism at any point, either from lack of, or inadequate supplies of, the factors involved in these reactions, will lead to a non- or slowly coaguable blood; hæmostasis can thus only be brought about or accelerated by supplying the deficient factor.

NATURAL HÆMOSTATIC SUBSTANCES

Prothrombin is formed in the liver from the K-vitamins which are substituted 1:4-naphthoquinones; there is evidence for the existence of more than one prothrombin. It is a white, water-soluble, amorphous protein containing some carbohydrate in its molecule, and whilst it is easily inactivated in aqueous solution it remains stable as a dry powder. Prothrombin is a potent reagent, and after activation with thromboplastin (and probably certain snake venoms) will clot fibrinogen or blood rapidly. Clinically, deficiency of prothrombin leads to hæmorrhagic disease of the newborn (hypoprothrombinæmia), and may be found in obstructive jaundice, cirrhosis of the

CURRENT THERAPEUTICS

XXIV.—HÆMOSTATICS

By JOHN F. WILKINSON, M.D., M.Sc., Ph.D., F.R.C.P., F.R.I.C.,
Physician and Director, Department of Hæmatology, Manchester Royal Infirmary.

COAGULATION of the blood is normally an emergency function to prevent loss of blood from the body. Excessive hæmorrhage, however, may arise from both intrinsic and extrinsic causes, and failure to control bleeding usually leads to severe secondary anæmia, anoxæmia, shock, and ultimately, death.

Apart from hæmorrhage due to trauma, I have discussed previously (*The Practitioner* 1940, 145, 382) the hæmorrhagic diseases due to important abnormalities of the blood that give rise to defects in the clotting mechanism. In these latter patients correction of the clotting defect by the addition of the deficient factor should produce satisfactory hæmostasis, but obviously may not necessarily play an adequate part in controlling traumatic hæmorrhages. Whilst it is convenient to consider the clotting mechanism of the blood as a hæmostatic process it should, nevertheless, be appreciated that in the body this phenomenon has other functions that do not call for discussion here.

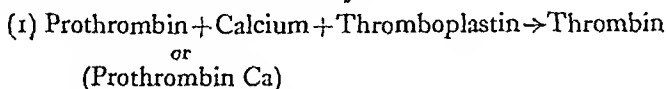
THE MECHANISM OF BLOOD COAGULATION

The circulating blood contains about 55 per cent. of plasma, in which the cellular constituents are suspended. When normal blood is shed or a blood vessel wall is damaged, the blood soon gels because of the precipitation of the insoluble protein, fibrin, which enmeshes the cellular constituents of the blood, and especially the increased numbers of sticky agglutinating platelets; ultimately becoming firmer, this gel contracts to a firm strong clot, squeezing out pale yellowish, unclottable serum, and sealing the bleeding point. If there is only slight injury to smaller capillary walls the adhesive platelets agglutinate at that site and seal off the leak before much or any bleeding can occur.

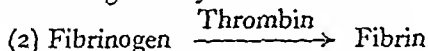
The mechanism of this fibrin formation is important and depends upon a sequence of chemical reactions that may be slowed down, at least *in vitro*, by lowering the temperature, by collecting the blood in vessels with inert surfaces, such as paraffin, wax, collodion, silicose, plastics, or by the addition of substances such as salt and magnesium sulphate, whilst complete inhibition is produced by the addition of citrates, oxalates or tissue extracts containing heparin. On the other hand, clotting can be accelerated by raising the temperature, by the passage of the blood through a rough or damaged vessel wall or tissues, or over foreign surfaces (e.g. glass), or by

the addition of suitable coagulant tissue extracts, or of protein substances such as trypsin or snake venoms.

Whilst many of the details of blood coagulation are not clear, the process depends essentially upon at least two main reactions involving prothrombin—calcium and fibrinogen in the plasma and thromboplastin from the platelets and damaged tissues. It is not now believed that heparin plays any significant part. Now this scheme postulates that thromboplastin, liberated from disintegrating platelets or tissue cells when the vessel walls are damaged, initiates the reaction whereby prothrombin is converted to thrombin in the presence of calcium. This latter is present in the plasma, but some believe that prothrombin itself is combined with calcium. Thromboplastin is thought by many to act as a catalyst, but there is some evidence that it acts stoichiometrically:—



When sufficient thrombin has been formed the next main reaction is a catalytic one, in which fibrinogen already present in plasma is converted probably through a loose fibrinogen-thrombin complex to insoluble fibrin, which can be seen under the microscope to be precipitated as long needles in the gel, which contracts gradually to a firm clot:—



The thrombin being an enzyme remains unchanged after this reaction, and so a very small amount is capable of converting a very large amount of fibrinogen, although much of it is absorbed or enclosed within the clot. There are other side-reactions occurring simultaneously but they do not concern us here, e.g. inactivation of prothrombin by the excess thrombin, effects of antithrombin, removal of thrombin by combination with possibly serum albumin. It is obvious that failure of this mechanism at any point, either from lack of, or inadequate supplies of, the factors involved in these reactions, will lead to a non- or slowly coaguable blood; hæmostasis can thus only be brought about or accelerated by supplying the deficient factor.

NATURAL HÆMOSTATIC SUBSTANCES

Prothrombin is formed in the liver from the K-vitamins which are substituted 1:4-naphthoquinones; there is evidence for the existence of more than one prothrombin. It is a white, water-soluble, amorphous protein containing some carbohydrate in its molecule, and whilst it is easily inactivated in aqueous solution it remains stable as a dry powder. Prothrombin is a potent reagent, and after activation with thromboplastin (and probably certain snake venoms) will clot fibrinogen or blood rapidly. Clinically, deficiency of prothrombin leads to hæmorrhagic disease of the newborn (hypoprothrombinæmia), and may be found in obstructive jaundice, cirrhosis of the

liver, toxic hepatitis, and after excessive dicoumarol therapy. Normal blood coagulation in these cases is therefore secured by administration of vitamin K orally or parenterally, but this takes several days for effective action.

Thromboplastin (or thrombokinase) is present in large quantities in tissues such as lung, as well as in platelets. It is deficient in thrombocytopenic purpura, in which condition there is gross reduction in the number of platelets, and in hæmophilia, in which the platelets are much less fragile, so that insufficient thromboplastin is liberated and consequently blood clotting is delayed, with great prolongation of bleeding. Because of the greater availability of potent thrombin preparations, thromboplastin is rarely used clinically.

Thrombin is also a water-soluble protein containing carbohydrate and is easily inactivated by heat, acids, alkalis, and heavy metal salts. It is prepared commercially from bovine or human plasma. It is such a powerful hæmostatic—accelerating extremely rapidly the conversion of fibrinogen to fibrin—that it must never be given to patients intravenously or intramuscularly, owing to the grave risk of immediate intravascular clotting. It is intended for topical application only.

Thrombin is prescribed as a dry powder which is dissolved in sterile isotonic saline solution just before use, but should not be stored in solution for more than a few hours. The strength of solution used varies between 25 to 1000 units per ml.: the stronger for immediate hæmostasis; weaker solutions according to its use in different types of surgical procedures. It has numerous uses owing to the speed with which it will initiate clotting of blood. Thus, after transurethral prostatectomy, gauze soaked in thrombin solution has been used for packing the prostatic cavity for twenty-four hours, whilst other users irrigate the bladder with a 10 ml. solution containing 1000 units per ml., which is left *in situ* for thirty to sixty minutes. For gastro-duodenal hæmorrhages, oral administration of a thrombin solution, containing 10,000 units in 33 ml. of phosphate buffer solution, has been efficacious after a preliminary washout of the stomach with 1/7 molar phosphate solution at pH 7.6 to reduce any acidity that would inactivate the thrombin. Thrombin has been most valuable in the treatment of surface bleedings, such as in superficial wounds, bleeding from the gums in hæmophilia, after tonsillectomy, and particularly in skin grafting on both the donor and the recipient areas. The surface is swabbed free from blood and the thrombin solution may then be sprayed on to the surface, or the area may be flooded with the solution through a fine needle. Powdered thrombin may be dusted on these surfaces or used in bone operations, besides being packed into cavities such as tooth sockets. The treated surfaces should not be swabbed afterwards, in order to avoid dislodging the clot. There is apparently no risk of sensitization following the use of bovine thrombin.

When using thrombin as a hæmostatic it is essential to emphasize certain points: it is a very powerful blood-clotting agent, for a solution of 1000

units per ml. will clot fresh blood instantaneously and, as already mentioned, it must *never* be injected either intravenously or intramuscularly. For efficient results the solution must come into immediate direct contact with the bleeding points, and so all old clot must be removed from the bleeding surface; this applies especially to tooth cavities. Although thrombin is usually applied as a solution (25 to 1000 units per ml.) or as a dry powder, it is often more effective, and indeed it may be advisable, to apply the thrombin solution with some mechanical support. For this purpose, gauze may be used or, better, an absorbable hæmostatic agent, such as gelatin sponge, oxidized cellulose, or fibrin foam, which after being soaked in the fresh thrombin solution can be applied directly to the bleeding areas after quick removal of old clot and blood.

Fibrinogen deficiency occurs only rarely in certain liver diseases and in constitutional fibrinogenopenia. It is formed in the liver, is soluble in water, but its use as a hæmostatic is not of great practical clinical importance *per se* for ordinary purposes. It has been used for nerve and skin suture by fibrin fixation, and in skin grafting to fix the graft, for example, the areas being flooded with plasma or fibrinogen solution and then clotted by the addition of thrombin solution.

ABSORBABLE HÆMOSTATIC AGENTS

So far, I have considered only those normal constituents of plasma, deficiencies of which lead to hæmorrhagic states which can usually be relieved by the appropriate replacements. But many situations arise, such as in traumatic hæmorrhages, when hæmostatics are urgently needed in greater amount and with quicker effect than can be obtained even with normal blood. In these cases even a powerful thrombin solution may be inadequate without additional mechanical help. (Of course it is assumed that the usual methods of pressure, ligature of obvious bleeding points and other surgical procedures have been employed.) Innumerable substances have been recommended and tried in the past but without any permanent success; in recent years new hæmostatic agents have been produced, and among these are the so-called absorbable hæmostatic agents, the use of which will now be considered. These agents are prepared in the form of gauze, foam, or sponge, which can be applied to the bleeding surfaces with or without preliminary soaking in thrombin solution. They are absorbed from the tissues and can therefore be left *in situ* without disturbing formed clots.

Oxidized cellulose.—Controlled chemical oxidation of cellulose gauze, "wool", and other forms, leads to its conversion into a polyanhydroglucuronic acid ("oxidized cellulose") which, whilst apparently having the same appearance as the original material, is both hæmostatic and completely absorbable in the tissues. The texture of this oxidized cellulose may be slightly coarser but is more compact and pliable than the original cellulose; it is much more soluble in dilute alkali and whole blood but, being unstable

to heat, it cannot be sterilized by autoclaving and should not be kept in a heated store. The gauze, soaked in thrombin solution, is applied directly to the bleeding surface or into the cavity, after removal of old clot and blood, and is pressed into close apposition with the bleeding point. It can apparently be used in incised organs and visceral beds and in non-infected wounds, which may be closed without drainage. When saturated with blood, oxidized cellulose becomes sticky, swells into a dark brown gelatinous mass, and fills the irregular contours of the wound and cavities, so exerting further pressure on the bleeding points. The cellulose gauze disintegrates rapidly in the course of twenty-four to forty-eight hours and is easily absorbed, or it may be removed by gentle scraping or simple irrigation; it does not become incorporated in scar tissue. The hæmostatic effect of oxidized cellulose is said to be due to its stickiness and property of swelling, with the ultimate formation of a coagulum consisting of hæmoglobin, salts of polyanhydroglucuronic acid, and fibrin. Its use is as a hæmostatic and it is not suitable for ordinary surface wound dressing. Oxidized cellulose is said to be less valuable as a hæmostatic and less absorbable in clean bone surgery, as it delays callus formation. Infection, of course, impairs its hæmostatic action. A practical point to remember is that oxidized cellulose, being an acid, should first be neutralized by soaking in sodium bicarbonate before saturating it with the solution of thrombin, which is inactivated by acids. This absorbable cellulose gauze used in conjunction with thrombin solution is a strong hæmostatic combination, and it has had extensive trials in general and neurological surgery of all types, in addition to a number of hæmorrhagic conditions. It cannot be used in association with penicillin, which it inactivates.

Fibrin foam.—Fibrin foam is a creamy-white to slightly brown preparation made from human or bovine thrombin and fibrinogen and resembles sheet sponge, which can be cut to size and shaped without difficulty. It is very light in weight, porous and easily crumbled between the fingers. As a rule it is used most effectively in conjunction with thrombin solution, of which it absorbs about 30 times its own weight, forming a most powerful hæmostatic agent; this can then be flattened out by gentle pressure for firm application to the bleeding surfaces. The thrombin solution is prepared (usually 25 to 50 units per ml.) with the usual sterile precautions, and the fibrin foam, cut to the requisite size, is immersed in it for a few minutes until thoroughly wet. It is then applied to the freshly swabbed bleeding surface or wound and held in place by gentle pressure, applied preferably through a superimposed cotton or gauze swab. Any excess moisture is removed, and after about one minute, clotting will have taken place and the foam will be adherent to the site. If this should accidentally be dislodged a fresh piece of prepared foam must be used. It has been employed widely in neurosurgical and orthopædic operations, general abdominal and chest surgery, especially when organs like the liver, kidney and lungs are involved, and it has been of great value in the treatment of hæmophilic hæmorrhages. Fibrin foam is gradually

absorbed from the tissues in the course of several weeks. It does not apparently interfere with bone healing or inactivate penicillin, and thus presents advantages over oxidized cellulose.

Gelatin sponge consists of a sterile, white non-elastic sponge obtained by drying a whipped-up foamy gelatin solution, with subsequent sterilization. It can be cut readily into the required shape and size and, unlike fibrin foam, will withstand relatively rough handling. It is used with or without saturation with thrombin solution. The sponge is applied to bleeding surfaces or cavities and can be packed into brain tumour cavities or used in other neurosurgical, orthopædic or general surgical procedures. It also has been employed extensively, with much success. For use, the gelatin sponge is cut to the requisite size and placed in sterile normal saline or thrombin solution. The air is expelled by gentle pressure with a spatula, and then the sponge is applied to the bleeding point firmly for a minute or so until it becomes adherent. It is absorbed naturally by phagocytosis. Gelatin sponge does not inactivate penicillin; it is stable to, and can be sterilized by, heat, and it does not possess antigenic properties. It is apparently much easier to prepare and apply than fibrin foam and seems to be equally efficient. It offers great scope in the future when supplies become more readily available.

Calcium alginate.—Calcium alginate is precipitated by adding calcium chloride to a solution of sodium alginate (prepared from seaweed). It has been used for the preparation of alginate gauze, "wool", film, and powder, which have hæmostatic properties resembling the previously mentioned absorbable hæmostatics. Since it is stable to heat, it can be autoclaved, and it does not inactivate penicillin. For use, the wound or burn is cleaned and then covered or packed with alginate gauze, preferably wetted with a solution of sodium alginate, which is then sprayed *in situ* with calcium chloride solution. An immediate transparent film of calcium alginate is produced and dries in five to ten minutes, forming a firm, tough, plastic dressing. For small wounds this may be adequate to close them without the use of sutures. The various forms of calcium alginate can be used as already described, but I have also found it of value in the treatment of bleeding tooth sockets in hæmophilics. The old blood clot is cleaned out, and powdered calcium alginate added directly to the bleeding point, or alternatively, the sodium alginate solution is put in and then a few drops of calcium chloride solution added to produce in the socket an immediate gel, which is intermingled with the oozing blood and leads to satisfactory clotting. Gentle but firm pressure is applied to the socket contents by means of a pad and suitable splint.

SNAKE VENOMS

It has been known for a long time that trypsin and certain proteolytic snake venoms have profound effects in accelerating blood clotting. The venoms can apparently be divided into two groups:—(1) those, like the tiger snake venom

(*Notechis scutatus*), which resemble thrombin and are able to convert fibrinogen to fibrin; and (2) those capable of activating prothrombin, in the manner of thromboplastin, to produce thrombin; such is the Russell's viper venom. The latter has been used extensively in place of thromboplastin in Quick's method for the determination of prothrombin. This coagulant property of Russell's viper venom led to its use clinically, since it is active in very dilute aqueous solutions (1 in 10,000). It was found to be particularly valuable in the treatment of surface hæmorrhages (wounds, after tonsillectomy, and the like) or after tooth extraction in hæmophilics. The venom is supplied as a light powder which is dissolved immediately before it is required in sterile saline solution to a 1 in 10,000 dilution. This is only used externally and must not be given intravenously. Wool or gauze soaked in this solution, which can be warmed to 40° C., is then applied directly to the bleeding points, after old clots and blood have been rapidly wiped away. Firm pressure is applied until clotting has occurred. For tooth sockets, these must be cleaned quickly, the gauze plug pushed down, and a previously prepared splint fitted to apply firm pressure. In this manner excessive bleeding can often be prevented after dental surgery, even in patients with hæmophilia and other hæmorrhagic conditions.

CONCLUSION

Summarizing the present position, it appears abundantly clear that with its greater activity and special advantages thrombin, with or without the support of fibrin foam or gelatin sponge, will replace other hæmostatic agents as a most effective method of controlling traumatic, operative and deficiency hæmorrhages.

REVISION CORNER

EARLY DIAGNOSIS OF CARCINOMA OF THE UTERUS

THE incidence of carcinoma of the uterus is considerable: 4,372 women in England and Wales died from this disease in 1945. Cancer may arise in the body of the uterus, in the cervical canal, or in the squamous epithelium on the vaginal surface of the cervix. The type of carcinoma depends upon the epithelium from which it is derived: adenocarcinoma in the body and cervical canal and squamous carcinoma of the vaginal portion of the cervix. Cancer of the cervix is eight to ten times more common than cancer of the body of the uterus. The order of frequency is: (1) squamous epithelioma of the cervix; (2) adenocarcinoma of the body of the uterus; and (3) adenocarcinoma of the cervix. The order of malignancy is: (1) adenocarcinoma of the cervix; (2) squamous epithelioma of the cervix; and (3) adenocarcinoma of the body of the uterus.

The cure rate of carcinoma of the cervix in an early stage (stage I) is 70 per cent., whilst the cure rate of all operable cases of carcinoma of the body is between 65 to 90 per cent. When first seen, only 11 per cent. of the cases of carcinoma of the cervix are in stage I, whilst nearly 90 per cent. of the cases of carcinoma of the body are operable. Early diagnosis offers the greatest hope of cure, and will continue to do so in spite of future improvements in therapeutic methods. The clinical history and findings are entirely different in carcinoma of the body and carcinoma of the cervix.

CARCINOMA OF THE BODY OF THE UTERUS

Age incidence.—Carcinoma of the body of the uterus is a disease of later age-groups. The majority of cases occur between the age of fifty and fifty-nine years. The relative frequency of its occurrence as compared with carcinoma of the cervix increases as age advances, and at the age of seventy to seventy-five years carcinoma of the body is as common as carcinoma of the cervix.

Relation to menstrual life.—The disease is predominantly one of the post-menopausal period. In only two out of 147 cases recorded by Donald and Fletcher Shaw was the disease pre-menopausal.

Relation to child-bearing.—In this same series of cases 52 per cent. were nulliparous, a relatively high incidence when it is taken into account that most post-menopausal women are parous. The remaining 48 per cent. had had one or two children many years before the onset of the disease.

Predisposing factors.—The woman who has irregular or profuse bleeding at the menopause is three-and-a-half times more likely to develop cancer of the body of the uterus than the woman who has neither irregular nor profuse bleeding. According to some authorities the occurrence of fibroids increases the likelihood of cancer of the body.

Symptoms.—Vaginal bleeding is the cardinal symptom. The patient may complain of bleeding or of a blood-stained discharge. Rarely the patient complains of a foul-smelling discharge with no bleeding. The important point to note about the bleeding is its tendency to be, or become, persistent. The bleeding with few exceptions is post-menopausal. Statistics show that four out of ten patients who complain of vaginal bleeding one year or more after the menopause have a cancer of the uterus, and it is therefore wise to consider every case of post-menopausal bleeding as malignant until the possibility of its being so has been eliminated. Pain occurs in a small percentage of cases but it is not an outstanding feature in the early stage.

Local physical signs.—These may be few; the cervix is healthy; a polypus may protrude at the os, but this does not eliminate the possibility of cancer of the body of the uterus; the uterus is regular in outline and in some cases it may be slightly enlarged; it is not tender and in the majority of cases is mobile. The appendages are rarely palpable. The final diagnosis can only be made by curettage.

CARCINOMA OF THE CERVIX

Age incidence.—This is a disease of middle life. In a series of 1200 cases analysed by Maliphant, 34 per cent. were in the decade forty-five to fifty-five, 30 per cent. were under forty-five, whilst 36 per cent. were over fifty-five. The risk of the disease increased enormously in the age-group thirty to thirty-four as compared with the age-group twenty-five to twenty-nine, and at the ages thirty-five to thirty-nine it is more than twice as high as at the ages thirty to thirty-four.

Relation to menstrual life.—The disease occurs in two-thirds of cases during menstrual life.

Relation to child-bearing.—In Maliphant's series 5 per cent. of the patients were nulliparous and 95 per cent. parous. Maliphant believes "that women with many children suffer from cervical cancer more frequently than do women with few children or only one child and that the relative risk increases slightly with each confinement, so that the woman who has six or more children is exposed to a risk twice as great as the woman who has had only one child".

Predisposing factors.—Married life and child-bearing are the predisposing factors, with the exception that this disease is rare in Jewish women.

Symptoms.—The sign which brings the patient for diagnosis is vaginal bleeding in one form or another; usually bleeding on coitus, douching or defaecation. Rarely (14 per cent.) the first symptom is pain in the back, groins or lower abdomen. Pain usually means either extension or secondary infection and has a bad prognostic significance. By the time the patient has bleeding and pain the disease is in an advanced stage in 90 per cent. of the cases. It is important to remember that there are no early symptoms.

Local physical signs.—If the patient has vaginal bleeding, a small, nodular, granular area may be found at the external os, but more often vaginal examination reveals either a friable, ulcerating, cauliflower-like growth coming from one lip of the cervix, or an ulcerating mass partially or wholly replacing the cervix. If the tumour is an endocervical carcinoma there may be a friable mass at the external os and enlargement of the cervix. The cervix will probably be immobile and there may be thickening of the fornices. The uterus may be normal in size or enlarged. Bleeding will occur following examination.

Diagnosis.—The friability, bleeding and position of the tumour leave little doubt as to the diagnosis. Additional aids to diagnosis in doubtful cases are (a) the use of a colposcope to view the cervix, this gives ten times the normal magnification, and (b) the application of Lugol's iodine to the cervix. Cancerous and pre-cancerous tissue remains relatively unstained by iodine, whilst normal cervical and vaginal epithelium, which contains glycogen, takes on a mahogany colour. These tests are of slight value. The best diagnostic procedure in doubtful cases is a biopsy.

VAGINAL SMEAR TECHNIQUE IN DIAGNOSIS

For some years smears of vaginal secretion have been used to diagnose the activity of the sex hormones. Papanicolaou in the course of his investigations discovered that cancer cells could be recognized, and further, that the presence of these cancer cells was a reliable means of diagnosis, not only in well-established but also in early stages of the disease.

In a series of between 7000 and 10,000 vaginal smears prepared from 3014 adult women, most of whom were in the cancer-bearing age of life, 179 were found to have cancer of the uterus. There were 127 cases of carcinoma of the cervix and, what is very important, 7 of these were early intradermal lesions of the squamous epithelium and nearly all of these 7 were invisible on close inspection of the cervix. There were 4 negative smears in the 127 cases of carcinoma.

The advantage of this method is that several hundred women can be examined periodically with little discomfort. In America this method is employed at "cancer

finding" clinics. At Boston City Hospital all departments referred women over thirty-five years of age for "screening". This screening consisted of a full history, pelvic examination, speculum examination and examination of a smear taken from the posterior fornix.

In 639 cases, in which 934 smears were examined, 54 cases of carcinoma of the uterus were found. Vaginal smears were positive in 51 of the 54 cases, carcinoma was clinically obvious in 42 and suspected and confirmed by biopsy in 6; in the other 6 it was unsuspected clinically but was diagnosed primarily by examination of smears and confirmed by biopsy. There were 12 false positive smears in 585 patients found not to have cancer.

The exact place of vaginal smear technique, whether that of Papanicolaou or of the phase-contrast microscope, in diagnosis is still indefinite. It has not yet replaced the biopsy, but it has in many instances pointed to the need for a biopsy and thus is a distinct advance in the field of diagnosis. The average woman wants to know if she has cancer or if she is likely to develop it. The first question can be answered by taking a careful clinical history, making a vaginal examination, a speculum examination of the cervix and, where facilities are available, by examining a vaginal smear. These examinations should be repeated at six- or twelve-monthly intervals during the cancer-bearing age. This procedure is advocated to ensure early diagnosis in view of the fact that symptoms in the early stages are absent in 90 per cent. of the cases. The second question, "is she likely to develop cancer", is not so easily answered. The predisposing factor to carcinoma of the body is low fertility, and to carcinoma of the cervix, multiparity, factors which cannot be altered. There is some evidence to suggest that treatment of cervicitis and cervical lacerations which commonly follow child-bearing, might decrease the incidence of carcinoma of the cervix. Smith, Smithwick and Rogers state that of 550 cases of cancer of the cervix, none gave a history of cauterization, and that of 1,150 in whom cauterization had been carried out from January 1914 to January 1927, not one was known to have developed cancer. Further, there is a time lag of between ten and thirty years between the birth of the child and the appearance of carcinoma. It would appear desirable during this time to "screen" the patient at regular intervals.

GLADYS H. DODDS, M.D., F.R.C.S., F.R.C.O.G.

THE TREATMENT OF THREATENED ABORTION

ABOUT 80 per cent. of miscarriages occur during the first third of pregnancy, and the third month is the most critical time. After the twelfth week the placenta is fully localized, and the anchoring villi of the chorion become more securely attached to the maternal decidua. From this time onwards the placenta is a more important source of oestrogens and progesterone than the corpus luteum, and the third month may be a transitional period during which the placental function is still uncertain.

SOME CAUSES AND THEIR TREATMENT

Those cases of miscarriage due to the rejection of a *malformed embryo* are usually inevitable. If a threat does not materialize the chance of foetal abnormality is small, and it is quite unjustifiable to refuse treatment for fear of the retention of an abnormal foetus.

Uterine abnormalities, such as fibroids, deep cervical lacerations, and minor congenital defects, may cause abortion, but are obviously untreatable during pregnancy. Although abortion in a first pregnancy is sometimes due to a minor degree of uterine hypoplasia, oestrogenic treatment would not be recommended at the actual time of bleeding, as the blood level of oestrogens is usually normal in cases of abortion, and there is no evidence that the uterus will respond any better to additional oestrogens. Such cases often succeed without treatment in a second pregnancy. In cases in which a *retroverted uterus* is discovered, correction is not advised while bleeding is in progress, unless there is retention of urine. It is doubtful if un-

complicated retroversion is a cause of abortion, and manipulative correction while bleeding is in progress will increase rather than diminish the risk of abortion.

In those cases in which abortion is due to some *maternal illness*, foetal death usually precedes expulsion, so that treatment is impossible; the damage is already done.

There remains the majority of cases in which the *cause of the abortion is obscure or hypothetical*, and I shall discuss these more fully. The decision whether or not to perform a vaginal examination is important. This should never be done without reason in cases of abortion, and always with full aseptic technique. If the patient is already known to be pregnant, and has only slight bleeding without pain, vaginal examination should be deferred until bleeding has ceased. If there is pain or severe bleeding the abortion is usually inevitable, so that examination will make matters no worse, and should be done both to assess the size of the uterus and dilatation of the cervix, information which will assist in the further management of the case; and also to exclude an ectopic gestation. In all cases in which bleeding, however slight, continues for more than two weeks, the cervix should be examined with a speculum, when some other cause of bleeding may be found, such as a cervical erosion or polyp.

GENERAL TREATMENT

Complete rest in bed remains the most important, if not the only, effective measure, and should continue for not less than five days after the loss ceases. The true importance of this must be impressed upon the patient, who so often imagines that some injection or vitamin is of greater or alternative value. Sedatives have no specific purpose save to allay apprehension and restlessness. Morphine is often prescribed to inhibit uterine contractions, and although large doses may do this temporarily, smaller doses increase uterine action, and it is doubtful if the ultimate outcome is affected by its use.

HORMONE THERAPY

The value (or danger) of corpus luteum hormone in cases of threatened abortion has been much discussed. Until recently it was thought to inhibit contractions of the uterus. Although this is the case in certain species it is not true for the human uterus, and many clinicians have remarked on the increased uterine activity and expulsion of the ovum that may follow its use. It might still be useful for quite another reason—that it is essential for the maintenance of the decidua; and it may reasonably be prescribed in cases that have miscarried in previous pregnancy, but are not now bleeding. If bleeding is actually occurring it cannot be recommended; for it would not alter the decidua quickly, and if it increases uterine activity the total effect will be more harmful than useful. Progesterone is excreted in the urine as pregnanediol, but estimations of this substance have not assisted in either estimating the probability of abortion or of the need for progesterone. If it is decided that the corpus luteum hormone is to be given to maintain the decidua (which I would not recommend while bleeding is actually occurring) the most convenient form is "ethisterone" (anhydro-hydroxy-progesterone), in doses of 10 to 20 mg. daily by mouth. There seems to be no advantage in using chorionic gonadotrophin instead of progesterone; such effect as it would have would be by stimulation of the production of progesterone. It has also been suggested that oestrogens should be given simultaneously with progesterone, and there are theoretical grounds for this opinion, but at present it can only be said that the matter is under trial and investigation.

VITAMIN E

The administration of vitamin E in the form of wheat germ oil capsules, 5 minims (0.3 ml.) t.d.s., or in synthetic form as α -tocopherol, has also been much discussed. It is true that artificial vitamin E deficiency in rats will cause foetal death, due to changes in the yolk sac placenta, but the human placenta is of different (allantoic)

type, and there is no evidence that any ordinary human diet is deficient in this factor. Many contradictory clinical reports have been published, especially relating to cases of "habitual" abortion, and I can only state that the vitamin is harmless but of doubtful value in cases of habitual abortion, and useless in the relative urgency of threatened abortion.

CONCLUSION

The reader may well conclude that there is no effective treatment for threatened abortion except rest, and this is not far from the truth. If partial separation of the ovum has already occurred, the most that we can hope to do is to prevent further separation, and it can hardly be claimed that any specific treatment will help. (I am not here discussing the wider question of "habitual" abortion.)

Finally, if the abortion does not become inevitable, the case should be followed carefully, to ensure that the uterus continues to enlarge, as otherwise a carneous mole may be unrecognized. In every case the patient requires further advice, stressing the importance of avoiding any local disturbance, such as intercourse, or any undue exertion, and maintaining optimal nutrition.

S. G. CLAYTON, M.D., M.S., F.R.C.S., M.R.C.O.G.

NOTES AND QUERIES

Sympathectomy for Cold Hands

QUERY.—I have suffered greatly all my life from very cold hands and feet, especially the hands, which remain cold even when I perspire elsewhere from walking in a temperature of 65° F. Consequently, I have painful chilblains in cold weather. Now, at the age of seventy-five, I hope to obtain relief by undergoing chemical sympathectomy. I shall be most grateful for your opinion on this method of treatment.

REPLY.—Chemical destruction of the sympathetic chain by blind injection has not, of course, the same precision as open sympathectomy, but in experienced hands the injection can be placed near the chain, and small quantities can be used, so that the chance of damage to important structures is minimized. The safety of the treatment is dependent upon the care with which it is carried out, and once the technique is mastered there is little danger of serious complications. Alcohol injections have been made for many years, and aqueous phenol injections for two-and-a-half years, and there is no evidence that late complications develop. The principal immediate trouble is neuritis, and both alcohol and phenol can produce it. As a rule it lasts only a few weeks, but occasionally may drag on for several months. Every effort must be made to keep the injection away from the spinal nerves, and this is particularly important in upper limb blocks, as the sympathetic chain here lies very near these nerves. Against this drawback must be considered the fact that lasting sympathetic interruption can be obtained in a few minutes without the need

for confinement to bed. The effect can last for many years, but it is probable that there is some return of sympathetic activity in the majority of cases after several months. The injection can easily be repeated to renew the sympathetic interruption. On the whole, open sympathectomy is still advisable in those young and fit enough to stand it, provided the lesion justifies this procedure. In other cases chemical sympathectomy is a most valuable substitute.

H. A. HAXTON, M.D., CH.M., F.R.C.S.

Hirsuties of the Upper Lip

QUERY.—I should greatly appreciate advice in the case of a woman patient, aged forty-seven, single, who has suffered for many years from a growth of hair on the upper lip. She has always been self-conscious about it, but she now says that it is "getting her down". Otherwise she has led a normal life in business.

REPLY.—A growth of hair on the upper lip in a woman of this age is sometimes a familial affliction, but more often develops about the menopause, when it presumably results from the diminution in the production of female sex hormones. In a few cases, disease of some part of the endocrine system can be identified. The existence of an abnormal endocrine state should always be considered, but endocrine treatment is not indicated, nor is it likely to succeed, unless there is clear evidence other than the *hirsuties* of endocrine upset. Even when endocrine imbalance can be demonstrated, treatment with hormones is not always successful.

In the great majority of cases the treatment

complicated retroversion is a cause of abortion, and manipulative correction while bleeding is in progress will increase rather than diminish the risk of abortion.

In those cases in which abortion is due to some *maternal illness*, foetal death usually precedes expulsion, so that treatment is impossible; the damage is already done.

There remains the majority of cases in which the *cause of the abortion is obscure or hypothetical*, and I shall discuss these more fully. The decision whether or not to perform a vaginal examination is important. This should never be done without reason in cases of abortion, and always with full aseptic technique. If the patient is already known to be pregnant, and has only slight bleeding without pain, vaginal examination should be deferred until bleeding has ceased. If there is pain or severe bleeding the abortion is usually inevitable, so that examination will make matters no worse, and should be done both to assess the size of the uterus and dilatation of the cervix, information which will assist in the further management of the case; and also to exclude an ectopic gestation. In all cases in which bleeding, however slight, continues for more than two weeks, the cervix should be examined with a speculum, when some other cause of bleeding may be found, such as a cervical erosion or polyp.

GENERAL TREATMENT

Complete rest in bed remains the most important, if not the only, effective measure, and should continue for not less than five days after the loss ceases. The true importance of this must be impressed upon the patient, who so often imagines that some injection or vitamin is of greater or alternative value. Sedatives have no specific purpose save to allay apprehension and restlessness. Morphine is often prescribed to inhibit uterine contractions, and although large doses may do this temporarily, smaller doses increase uterine action, and it is doubtful if the ultimate outcome is affected by its use.

HORMONE THERAPY

The value (or danger) of corpus luteum hormone in cases of threatened abortion has been much discussed. Until recently it was thought to inhibit contractions of the uterus. Although this is the case in certain species it is not true for the human uterus, and many clinicians have remarked on the increased uterine activity and expulsion of the ovum that may follow its use. It might still be useful for quite another reason—that it is essential for the maintenance of the decidua; and it may reasonably be prescribed in cases that have miscarried in previous pregnancy, but are not now bleeding. If bleeding is actually occurring it cannot be recommended; for it would not alter the decidua quickly, and if it increases uterine activity the total effect will be more harmful than useful. Progesterone is excreted in the urine as pregnanediol, but estimations of this substance have not assisted in either estimating the probability of abortion or of the need for progesterone. If it is decided that the corpus luteum hormone is to be given to maintain the decidua (which I would not recommend while bleeding is actually occurring) the most convenient form is "ethisterone" (anhydro-hydroxy-progesterone), in doses of 10 to 20 mg. daily by mouth. There seems to be no advantage in using chorionic gonadotrophin instead of progesterone; such effect as it would have would be by stimulation of the production of progesterone. It has also been suggested that oestrogens should be given simultaneously with progesterone, and there are theoretical grounds for this opinion, but at present it can only be said that the matter is under trial and investigation.

VITAMIN E

The administration of vitamin E in the form of wheat germ oil capsules, 5 minims (0.3 ml.) t.d.s., or in synthetic form as *α*-tocopherol, has also been much discussed. It is true that artificial vitamin E deficiency in rats will cause foetal death, due to changes in the yolk sac placenta, but the human placenta is of different (allantoic)

may save its life.

On the subject of induction, no over-all ruling can be given, beyond stating that in any case induction at the seventh month is so early that the potential risks to the child would be further increased by its prematurity. The mother's blood should be tested for antibodies each week during the last six weeks of pregnancy, and if they are found in increasing amounts the induction should be performed between the thirty-sixth and thirty-eighth week, according to the size of the child. The pathologist should be present when the baby is born and should immediately test its blood for evidence of anaemia and haemolysis. On these findings it would be decided whether a transfusion were necessary at all, and if so, whether a straight transfusion or an exchange transfusion would give the baby the greatest chance of survival. The factors which would lead to these respective tests cannot be given in detail in a brief reply to the query. The fact that there are such points to be considered is a further illustration of the advisability of a case such as this being handled where every possible facility can be provided.

JOHN STALLWORTHY, M.B., F.R.C.S., M.R.C.O.G.

Procaine Lactic Acid in Osteo- and Rheumatoid Arthritis

QUERY.—I shall be grateful if you can give any information on the use of procaine lactic acid in osteo- or rheumatoid arthritis, and the method of administration and dosage employed.

REPLY.—G. Waugh (Sunderland) uses procaine lactic acid in both chronic rheumatoid arthritis and chronic osteoarthritis, I think its use is best confined to the osteoarthritic group. The sterile solution is put up in ampoules, at pH 5. The solution is injected into the affected joint cavity, with the usual precautions and avoidance of intravenous instillation: for the interphalangeal joint, 1 ml.; for the wrist and shoulder, 2 to 4 ml; for the knee, 5 to 10 ml; and for the hip, 10 to 15 ml. are used. Afterwards, the joint is manipulated. The injections may be repeated at weekly or fortnightly intervals. In the osteoarthritic hip the procedure may be of considerable difficulty. About half the patients so treated derive marked benefit; this presumably results from stretching of the capsule and the subsequent manipulation. Severe febrile reactions are not unknown.

RALPH KAUNTZE, M.B.E., M.D., M.R.C.P.

PRACTICAL NOTES

Chloromycetin in Typhoid Fever

FOUR cases of typhoid fever, two children and two young adults, have been treated with chloromycetin by J.-J. Mozer, R. Audéoud and J. Delétra (*Revue Médicale de la Suisse Romande*, September 25, 1949, 69, 653). The dosage employed was: 1 g. initially, followed by 0.5 g. four-hourly; total dosage 19.25 g. In the two children, both confirmed cases of paratyphoid B, there was fall of temperature and cessation of diarrhoea after forty-eight hours. Chloromycetin was continued for four days. In the other two cases there was dramatic change in the symptoms twenty-four hours after institution of treatment, the temperature reaching normal on the third day. In one of these cases the drug was stopped on the third day, with resultant recurrence of symptoms four weeks later, which responded rapidly to further chloromycetin therapy. Dosage advocated by these authors is: 50 mg. per kg. body weight (average 3 g. for an adult) initially, followed by 0.25 g. every two or three hours. Treatment should be continued for five days after fall of temperature. A report of the use of chloromycetin in five cases of encephalitic typhoid and four cases of ordinary typhoid fever is given by E. Benhamou, A.

Albou, F. Destaing, and A. Sorrel (*Presse Médicale*, September 24, 1949, 57, 833). Dosage recommended is: 4 g. initially, followed by 0.25 g. two-hourly (in some cases 0.5 g.). In the five cases of encephalitic typhoid there was rapid fall of temperature and amelioration of symptoms. In spite of this, intestinal perforation occurred in one case and the patient died after operation. In another there was relapse and the chloromycetin was increased to 6 g. daily, and later aureomycin added; total dose of chloromycetin 60 g., and of aureomycin 7.5 g. In the four cases of ordinary typhoid fever a total dose of 7.5 to 26 g. of chloromycetin produced rapid fall of temperature by lysis and amelioration of symptoms in less than six days. In one case two intestinal hæmorrhages occurred necessitating blood transfusions; chloromycetin was continued and healing obtained in less than five days. The fact that intestinal perforation or hæmorrhage may occur during chloromycetin therapy, even during the afebrile stage, is emphasized by J. C. Patel, D. D. Banker and C. J. Modi (*British Medical Journal*, October 22, 1949, ii, 908), although these complications did not occur in their small series of six cases. Relapse, if the drug is not continued for a

consists of suitable physical measures. When individual hairs are thick and strong a permanent epilation with electrolysis is the most satisfactory treatment. It is tedious, and as only a limited treatment can be given at each session, the whole period of treatment usually extends over a few months. It has the advantage of being permanent. When growth of hair is fine and downy, electrolysis is not usually possible. In a dark-haired person it is often sufficient to bleach the hairs with hydrogen peroxide every few days. In other cases the hairs may be removed either by cutting with scissors or with clippers, or with an electric razor. It is extremely unlikely that either of these procedures encourages the growth of hair. There is no great objection to the use of depilatory creams, but they must be used with care in order to prevent irritation of the skin. Shaving with an ordinary razor, plucking, or epilation with wax are better avoided, as they may perhaps actually stimulate the further growth of the hair.

F. RAY BETTLEY, M.D., F.R.C.P.

Barrier Creams

QUERY.—I am a general practitioner and also Works Medical Officer at a large factory, and would be grateful if you could advise me on effective barrier creams. Is sulphonated castor oil of any value as a protective agent?

REPLY.—It is illogical to advise as to the suitability of any protective agent against a particular skin hazard, except with an accurate knowledge of the clinical and physical characteristics of such potential irritant. There can no more be a universal panacea for prevention of occupational dermatitis than there could be one antiseptic expected to destroy every form of bacteria. Your correspondent would be well advised to consult Innox Laboratories, 233 Balls Pond Road, London, N.1, who appear to be one of the few firms approaching the problem scientifically: barrier creams of a widely varying range are manufactured, each having its own particular contents designed against the skin irritant in question.

Sulphonated castor oil is a non-irritant and efficient cleansing preparation without degreasing or abrasive qualities; it is not a preventative, and its capacities are only applicable within a limited field. Its chief value may lie in the fact that it does not do the harm to the skin that many other substances do, such as soap, paraffin, turpentine, and sand.

P. B. MUMFORD, M.D., F.R.C.P.

Obstetric Management of a Suspected Case of Erythroblastosis

QUERY.—I shall be grateful to you if you can

help me regarding the management of a future confinement which will presumably be difficult. The patient, aged thirty, had her first baby in September 1948. It was a boy, deeply jaundiced at birth. Despite a blood transfusion (50 ml.) and massive doses of vitamin K intravenously, the baby died. The patient is now due for her second pregnancy, in February 1950. Blood tests have been done on the husband and wife with the following results:—

Husband = RH positive (D.pos.)

Wife = RH negative. No antibodies present

I have planned (1) to do the confinement at home, and (2) an exchange transfusion of the infant immediately after birth. However, the local pathologist is of the opinion that it would be better to do a surgical induction at the seventh month, followed by an exchange transfusion. What I want to know is: is it better to do an induction at the seventh month, followed by an exchange transfusion, or can I let the case run to full term and do an exchange transfusion immediately the baby is born?

REPLY.—There is important information which is not supplied in this query. The fact that the baby was deeply jaundiced at birth is suggestive of erythroblastosis, but it is most unusual for the first-born child to be affected *unless* the mother has previously been immunized either by an incompatible transfusion or by the injection of Rhesus-incompatible blood. Many women have been given intramuscular injections of blood in the past for a variety of conditions, and some have been immunized in this way. If the mother has not been immunized it is the more necessary to know what were the autopsy findings on the child before giving a prognosis for future pregnancies. The fact that no antibodies were detected when the mother's blood was last examined is a favourable sign. *It cannot be emphasized too strongly*, however, that the effective treatment of a baby born with severe erythroblastosis may tax to the utmost the combined skill of a team consisting of a pathologist, expert in blood conditions, an obstetrician, and a paediatrician. In departments in which exchange transfusions are performed the difficulties and dangers are fully realized, and there can be few authorities who would agree that the procedure is a reasonable one to be performed in the patient's own home by a general practitioner, however competent. I would therefore suggest that this patient should be referred to the nearest well-equipped Maternity Unit. If it happens that on this occasion a healthy infant is born, nothing will have been lost, but if once again the infant is affected, the facilities offered in a department

use of badly prepared tobacco. Nearly all the cases observed during the war period occurred in non-drinkers and moderate smokers. The onset is insidious, with scotoma which interferes with reading and precision work, but not with orientation. The scotoma is considerably more marked in the red test than in the blue, which is a useful diagnostic feature. The only rational treatment is abstinence from tobacco; if this is done sufficiently early, complete cure can be obtained in some weeks, or at the most months. Addition of vitamins to the diet is useless; nevertheless, a good diet with plenty of milk, vegetables, fresh fruit and wholemeal bread is advised. Mention is made of the American author Carroll, who has cured tobacco amblyopia with a rich diet without stopping either tobacco or alcohol; this is stated not to be astonishing, as a subject who is well nourished is able to support tobacco better than one on a poor diet. Finally, many of those suffering from tobacco amblyopia during the war have been able to resume smoking without developing any eye symptoms.

Streptomycin Therapy in Peritonitis

A REPORT on the results of a study of the use of streptomycin in a series of 85 cases of faecal peritonitis is given by E. J. Pulaski, A. B. Voorhees, and S. F. Seeley (*Annals of Surgery*, August 1949, 130, 242). Many of the more severely ill patients were given combined streptomycin and penicillin treatment. The cases were divided into two groups—spreading and local. Eighteen cases were treated with streptomycin alone; in this group results were good in 8 of the spreading type and in 4 of the local type; total good results 67 per cent.; negative 33 per cent. In 67 cases combined streptomycin and penicillin therapy was given; in the spreading type good results were obtained in 31, and in the local type in 20; total good results 76 per cent.; negative 24 per cent. The optimal dosage of streptomycin, whether alone or in combination, "seems to be at least 2.5 g. daily". After forty-eight hours it was usually possible to judge the success or failure of the streptomycin therapy, which should, however, be continued for at least forty-eight to seventy-two hours after return of temperature to normal. It is stated that: "In early spreading peritonitis in which the infecting organism originates in the gastro-intestinal tract, combined treatment with streptomycin and penicillin seems to offer no significant advantage over streptomycin alone. In the management of localizing lesions, on the other hand, combined therapy seems superior". The use of streptomycin in eleven cases of tuberculous peritonitis is recorded by

M. Gaafar and A. el Badry (*Journal of the Royal Egyptian Medical Association*, June-July 1949, 32, 483). Good results were obtained in all cases: the effect of the drug was rapid, the general condition showing marked improvement within two weeks, and there was no recurrence in any of the cases. The dose suggested is 1 to 2 g. daily for four to six weeks. The authors state: "Streptomycin is very effective in the treatment of tuberculous peritonitis even when it is complicated by lesions elsewhere . . . The total amount of streptomycin required to effect a cure in the case of peritonitis is much less than that needed to obtain definite improvement in other forms of T.B."

Flaxedil as a Curarizing Agent

H. B. WILSON and H. E. Gordon (*Lancet*, September 17, 1949, ii, 504) report on the use of the curarizing agent "flaxedil" [tri-(diethyl-amino-ethoxy)benzene triethiodide] in a series of 80 patients, 60 children and 20 adults, undergoing laparotomy (all the children and 8 adults), intrathoracic procedures, and one abdomino-perineal excision of the rectum. Following premedication with omnopon and scopolamine or omnopon and atropine, soluble thiopentone and nitrous oxide and oxygen were used as anaesthetics, and flaxedil was administered just as the surgeon reached the peritoneum, with additional doses as required, the last dose at least 30 minutes before the end of the operation. The following findings are recorded: (1) flaxedil, 120 mg., gave comparable clinical effects to those obtained with *d*-tubocurarine chloride, 15 mg.; (2) relaxation began 60-90 seconds after the intravenous administration of flaxedil, reaching its peak in 120 seconds, persisting for 20-25 minutes and wearing off gradually; (3) there was no fall in blood pressure; (4) no clinical evidence of excessive release of histamine; (5) no collapse and no distension of the gut; (6) no venous thromboses; (7) no abnormal constituents in the urine; (8) postoperative sickness was minimal, although sedation was required earlier. A report on the use of the same drug (named 3697 RP) is given by P. Huguenard (*Bruxelles-Médical*, September 25, 1949, 29, 2059), who states that 3697 RP is less toxic than *d*-tubocurarine, and secondary neuro-vegetative effects are practically nil, bradycardia and hypotension being very rare, salivation and redness of the face only slight, and sweating non-existent. The dosage recommended by this author is 1 mg. per kg. body weight initially, followed by further doses at 30 to 50 minute intervals if necessary. The drug does not precipitate the action of barbiturates, and in pentothal anaesthesia should be

sufficient period, may also occur: in one case this happened after an afebrile period of twelve days, and the blood culture became positive during the relapse. The total dosage aimed at was 18 g., but owing to shortage of the drug only one patient received this dose. Two of the three patients who recovered received total doses of 12 g. and 16 g. respectively, but one had a relapse. The average duration of fever after institution of chloromycetin therapy was 1.5 days, and the average afebrile course 12.5 days. The authors conclude: "We believe that the drug is the most effective therapeutic agent available at present against typhoid fever . . . However, an extensive controlled trial is necessary to determine the optimal dose".

Local Urea Therapy in Dendritic Ulcer

THE results obtained in a series of 33 cases of dendritic ulcer by the local application of a 25 per cent. urea solution are recorded by M. Klein and S. J. H. Miller (*British Journal of Ophthalmology*, October 1949, 33, 643). The eye was anesthetized with two instillations of 0.5 per cent. amethocaine hydrochloride B.P. With the patient either sitting or recumbent, a contact lens applicator was placed over the eye and filled with freshly made 25 per cent. urea solution, 2 drops of amethocaine being added to each 5 ml. of solution. During the treatment the eye was observed through the transparent plastic applicator to ensure the ulcer being covered by fluid; if this was not so, the applicator was replenished. The duration of treatment was five minutes. If there was difficulty in using the contact lens applicator a bakelite eye-cup, with the bottom removed, was substituted, with the patient recumbent, the urea solution being poured into the cup after it had been placed over the open eyelids. Slight pressure of the cup kept the palpebral fissure open and ensured the cornea being bathed with fluid. After application of the urea solution, 1 per cent. atropine drops were instilled, yellow soft paraffin was placed in the lower fornix, and the eye bandaged. The dressing was changed after twenty-four hours. A second or third treatment could be given after an interval of twenty-four hours. The cases were divided into three groups: (1) 22 cases with well-localized dendritic figure; (2) 8 cases with more extensive lesions; (3) 3 cases with deeper lesions. In group 1 the number of days before healing occurred was 2-16, average 8. In 20 of these cases one application of urea proved sufficient. In group 2 the healing time was from 7 to 14 days, average 15.5. In group 3 the healing period in two cases was six weeks, and in one 28 days.

Dramamine in Radiation Sickness

THE results of an investigation into the value of dramamine (*beta*-dimethylaminoethyl benzo-hydryl ether 8-chlorothecophyllinate) in 82 cases of radiation sickness are reported by J. W. Beeler and his colleagues (*Proceedings of the Staff Meetings of the Mayo Clinic*, September 14, 1949, 24, 477). They are summarized in the following table:—

Results	Dramamine		Control	
	Cases	Per cent.	Cases	Per cent.
Excellent	21	25.6	0	0
Good ..	44	53.7	3	13.0
Fair ..	4	4.9	9	39.1
Poor ..	13	15.8	11	47.9
Total ..	82	100	23	100

The usual dose was 100 mg. of dramamine thirty to sixty minutes before irradiation, repeated one-and-a-half and three hours after treatment, i.e., a total dosage of 300 mg. In some cases a total dosage of 200 mg. was sufficient, whilst in others 400 mg. were required. In very severe cases it was found useful to supplement this dosage with 200 mg. of pyridoxine intravenously. The side-effects of dramamine consisted of drowsiness (15 cases), "bad taste" (8 cases), paresthesia (2 cases), and nausea (1 case). It is concluded that "this inexpensive drug can be safely used both as therapeutic and a prophylactic agent in the treatment of radiation sickness". In discussing this report, J. H. Tillisch (*Ibid.*, p. 482) suggests that "a theory that might explain the action of the drug in both motion and radiation sickness is that the drug has a specific depressant effect on the vomiting reflex".

Chronic Tobacco Intoxication

THE chief symptoms of tobacco intoxication are amblyopia and neuritis. Although formerly alcohol was thought to play a part in the genesis of tobacco amblyopia, it has now been found to occur among non-drinkers, and conversely neuritis occurs in non-smoking alcoholics. These facts are pointed out by R. Weekers (*Revue Médicale de Liège*, October 1, 1949, 4, 573), who discusses contributory factors and treatment. During periods of famine and malnutrition there is a considerable increase in the incidence of nicotine neuritis, and also tobacco amblyopia. These facts were confirmed in Belgium during the recent war: the incidence rate of tobacco amblyopia at the Ophthalmic Clinic, University of Liège, increased from 1 to 3.4. Since 1945 the condition has become rare. The increase was attributed to insufficiency of calories, and was also probably due to the

REVIEWS OF BOOKS

Ophthalmic Medicine. By JAMES HAMILTON DOGGART, M.D., F.R.C.S. London: J. & A. Churchill Ltd., 1949. Pp. x and 329. Figures 87 and 28 coloured plates. Price 32s.

UNTIL recently no textbook on medical ophthalmology has been published in Great Britain since 1925. This new work is therefore most welcome. Whilst covering the subject from the standpoint of the ophthalmologist, it avoids the temptation of straying too far into the realms of neurology and it does not attempt to be a reference textbook. Its readable style will appeal to candidates for the Diploma of Ophthalmology and to general practitioners. The illustrations are in general good but could perhaps be even more numerous. The references at the end of each chapter include the titles of articles of value to candidates for the Fellowship of the Royal College of Surgeons, and others desiring fuller information on particular subjects. The general production is good.

Fundamentals of Otolaryngology. By LAWRENCE R. BOIES, M.D. Philadelphia and London: W. B. Saunders Company, 1949. Pp. xv and 443. Figures 184. Price 32s. 6d.

THE author states in his preface that this textbook is not only designed to offer basic instruction to undergraduate students, but to provide fundamental information to the physician who is not a specialist. The book is beautifully produced and well illustrated, and those diagrams designed to clarify complicated anatomical relationships of the middle ear tract must be particularly commended. The author's idea of what a student should know is vastly different from that generally accepted in this country. Is he wrong or are we old-fashioned? Let us admit that penicillin and the sulphonamides have revolutionized treatment of infections of the middle ear tract and complications that arise therefrom, but even so it seems strange that lateral sinus thrombosis is dismissed in half a page, meningitis in one paragraph, and brain abscess in seven lines. On the other hand, a chapter is devoted to tinnitus; and vertigo, its causes, investigation and treatment are dealt with at the same length. It seems strange to British otologists that students should be taught modern views about Ménière's disease and yet should not be told about extension of chronic suppurative otitis media to the labyrinth. It might have been better if more explicit guidance were given in the recognition of, for instance,

circumscribed labyrinthitis secondary to cholesteatomatous attic disease. There are gaps which are difficult to condone: foreign bodies in the external auditory meatus are only mentioned as a possible cause of conductive deafness, and auditory nerve tumours as a possible explanation of tinnitus or vertigo.

The chapter on applied anatomy and physiology of the nose is excellently done, whilst the section on nasal allergy is sound without being too complicated. As regards acute and subacute frontal sinusitis, too little attention has been given to the importance of controlling coexisting antral infection. The section on laryngeal obstruction and the description of tracheotomy are good. The scope of endoscopy is clearly explained. The photographic illustrations of intrinsic carcinoma of the larynx are superb. This book will certainly interest the undergraduate student: it will help him to understand much of the routine work in an ear, nose and throat out-patient clinic, but it may well leave him without knowledge enough to satisfy examiners in this country.

Lehrbuch der Chirurgie. VOL. 1. EDITED BY A. BRUNNER, C. HENSCHEN, H. HEUSSER, A. JENTZER, O. SCHÜRCH, and J. VEYRASSAT. Basle: Benno Schwabe and Co., 1949. Pp. xix and 912. Figures 259. Price Sw. frs. 74.

THIS is the first volume of a textbook which (we gather) is to be completed by the second. The work is written by representative Swiss surgeons and is being published in both French and German. The preface states that as Switzerland is a small country in which there is scarcely room for pure specialists, care has been taken to have the articles on special subjects—urology, orthopaedics, neurosurgery, and the like—written by surgeons who have had general as well as special experience; by this means the editors have made sure that general surgical principles have not been swamped by too much detail. Wounds and surgical infections are satisfactorily dealt with. Penicillin is of course recommended for boils and carbuncles but the doses are on the low side and it is not surprising that it is found necessary to recommend the excision of some large carbuncles; if larger doses of penicillin were given there might be no need for operative interference. The section on tumours gives a clear account of their clinical course and treatment but does not deal with their histology. Diseases of the vascular and lymphatic systems are concisely described and there is an up-to-date account of the diseases of

administered some seconds before injection of the barbiturate. The use of 3697 RP (flaxedil) is recommended in surgery, and particularly for tracheal intubation and in the treatment of laryngospasm, in obstetrics (Caesarean, forceps), and in convulsive therapy.

Nasal Headache

W. M. MOLLISON (*Irish Journal of the Medical Sciences*, October 1949, Ser. 6, no. 286, p. 750) classifies nasal headaches under three headings: (1) headaches in connexion with the walls of the nose; (2) headaches in connexion with the paranasal sinuses; (3) neuralgic headaches. Headaches of group 1 type are stated to be most commonly due to pressure of the septum on the middle turbinal, or *vice versa*, although some sinus affection may complicate the obstruction and cause pain. Group 2 includes (a) headaches due to change in intra-sinus pressure; and sometimes the mere introduction of a needle into the antrum relieves the pain although no secretion is found. In the same way a small polypus plugging the sinus may cause pain. (b) Pain from negative or decreased pressure. In this subgroup are included the "vacuum" headaches of Sluder, caused by a narrow nose combined with hyperplastic changes in the soft parts and bones of the middle turbinals; should the narrow passage open, relief is experienced. The operation of submucous resection of the septum with or without removal of part of the middle turbinal relieves the frontal headache. A new type of headache has been introduced with aviation, i.e. "sinus barotrauma", in which as a result of rapid ascents and descents the patient experiences pain in the frontal region if any obstruction of the ostia is present. It is stated that "the moral in these cases is to avoid flying when there is any congestive condition of the nose, acute or chronic catarrh, or polyp". Factors causing sinus headaches are *vasomotor* and *allergic rhinitis*. Hersh, in a review of 1000 cases of headache in American recruits diagnosed 282 as due to vasomotor rhinitis, and also found that other nasal headaches were increased with superimposed vasomotor rhinitis. *Occipital headache* is one of the most common types and has been established as of muscular origin, i.e. muscular contraction. Occipital pain may also be due to chronic sinusitis, owing to the contracted state of the muscles. In group 3, in which the nasal headaches are due to neuralgia of the nerves which supply the walls of the nose and the sinuses, the headache is not of genuine nasal origin. It has been likened to Sluder's "lower half headache" which he considered was of vascular origin. Finally, the author states:

"though I do not consider that so-called nasal neuralgias are due to disease in the nose or the sinuses, I am convinced that damage to nerves as the result of nasal operations is often responsible for severe and lasting fifth nerve pain".

Intradermal Distilled Water Injections for Renal Colic

INTRADERMAL injection of distilled water at painful points was first practised by Schleich and Liebreich in 1885. G. di Maio (*Minerva Medica*, September 1, 1949, 40, 265) treated 19 cases of renal colic due to ureteral or renal calculus by this method. The painful points were carefully localized, and 1 ml. of distilled water was injected into the skin at each point. A greenish-white wheal, about 1 cm. in diameter, resulted, surrounded by a slightly hyperæmic area. During the injection and for one to two minutes afterwards the patients felt a burning pain. This disappeared after two to three minutes, and with it colic and vesical tenesmus. The effect lasted for hours or days and was always followed by expulsion of the gravel or calculus. Repeated injections always had the same analgesic effect. In a case of rheumatic lumbar myalgia the first injection was ineffective, but a second injection six hours later had the desired result. The author discusses the various theories of the mode of action of these injections and tends to attribute it to electrotonic depolarization, which produces a short circuit of the synaptic junctions across which the visceral painful stimuli are carried.

Ointment for Tinea Capitis

THE formula of an ointment for use in the treatment of ringworm of the scalp is given by H. Haber, R. T. Brain, and J. W. Hadgraft (*British Medical Journal*, September 17, 1949, ii, 626):—

"Salicylanilide	5 g.
Crill No. 6	10 ml.
Solution of citric acid 2 per cent. and sodium propionate 1 per cent.	2 ml.
Carbowax 1500	to 100 g.

Melt the carbowax 1500 over a water-bath, add the Crill No. 6, dissolve the salicylanilide in the mixture, add the solution of citric acid and sodium propionate, and allow to cool, stirring occasionally".

The hair of the entire scalp is cut very short; the scalp is washed every morning with soap and water, the affected parts being scrubbed with a soft nailbrush; and the ointment is applied to the lesions with a toothbrush and spread over the scalp. A linen cap is worn day and night.

Of twenty-seven cases treated—20 *M. felineum*, 6 *M. audouini*, 1 *Tr. sulphureum*—75 per cent. were cured, the cure period ranging from six to sixteen weeks. The case of *Tr. sulphureum* proved resistant to the treatment.

associates with the early pioneering days of the States. Equally striking is his devastating analysis of his idols, e.g. Osler, and of the institution of which he is a loyal and devoted member. For the author the four "great doctors" of the Johns Hopkins—Osler, Welch, Halstead and Kelly—are among the greatest names in medicine, and yet he does not hesitate to point out their foibles as well as their merits. This is not orthodox history but it makes fascinating reading.

NEW EDITIONS

Nutrition and Diet in Health and Disease, by James S. McLester, M.D. (W. B. Saunders Company, 45s.) has long been recognized as one of the best books on the subject. The fifth edition, which has just been published, well maintains this high reputation. A thorough revision of the whole book has been carried out, particularly in the sections on vitamins and protein, and new food tables have been added. The section on nutrition in disease has also been brought up to date, and now contains a full discussion of high protein diets in liver disease, and the fashionable sodium-free diet in hypertension.

Acute Injuries of the Head, by G. F. Rowbotham, F.R.C.S., in its third edition (E. & S. Livingstone Ltd., 35s.), has been brought up to date on the basis of the many advances in neurosurgery

during the war years. In his preface the author pays warm tribute to Sir Hugh Cairns, Professor Jefferson and Professor Dott for their outstanding services during the war. The new edition is beautifully produced and illustrated.

REWRITING of the chapter on the development of the early ovum, with new illustrations, is one of the features of the tenth edition of *A Synopsis of Obstetrics and Gynaecology*, by Aleck W. Bourne, M.B., B.Ch., F.R.C.S. (John Wright & Sons Ltd., 21s.). Penicillin in gonorrhœa, syphilis, salpingitis, ophthalmia neonatorum, and other conditions is among the new additions.

The Essentials of Chiropody, by Charles A. Pratt, in its second edition (H. K. Lewis & Co. Ltd., 10s. 6d.) has been brought up to date and some illustrations altered. The author, in addition to giving clear, illustrated expositions of the various chiropodical procedures, discusses miscellaneous disorders of the feet, such as athlete's foot, chilblains, sprains, and the like. This is a useful little book for the practitioner.

Training for Childbirth, by Minnie Randell, O.B.E., S.R.N., in its fourth edition (J. & A. Churchill Ltd., 10s. 6d.) contains among new material information on the expression of breast milk, breast feeding and the care of the breasts, and gas and air analgesia. There is a useful chapter on postnatal exercises.

NOTES AND PREPARATIONS

NEW PREPARATIONS

CIMLAC GAUZE is a woven fabric impregnated with a sterilized glyco-gelatin mass containing 5-amino-acridine and hexylresorcinol, both of which are active against gram-positive bacteria and *Ps. pyocaneus*. Rapid control of infection and speedy healing are stated to occur when cimlac gauze is used as a dressing for burns, wounds, boils and carbuncles, varicose ulcers, and impetigo. The gauze is supplied specially packed between two layers of cellulose film to facilitate "non-touch" application. (Calmic Ltd., Creve Hall, Cheshire.)

DOBAGEN non-staining gentian violet cream (gentian violet and zinc sulphate, each $\frac{1}{2}$ per cent., salicylic acid 2 per cent. approx.) has been prepared for the treatment of epidermophytosis. Advantages claimed for this cream are its non-staining property and quick absorption by the skin. (Forsters [Pharmaceuticals] Ltd., Seaham, Co. Durham.)

LABITON (L.A.B.) kola and vitamin tonic (Vitamin B₁, 7.5 mg.; alcoholic liquid extract of kola nuts, 35 ml.; syrup B.P., 30 ml.; glycerophosphoric acid 20 per cent., 0.25 ml.; flavouring and distilled water to 100 ml.) is stated to act as a stimulant to the central nervous system and as a general tonic in debility and convalescence. (Laboratories for Applied Biology, 6 Percy Street, London, W.1.)

PEDAFORM foot-bath concentrate contains pelargonic acid, formalin, and a detergent and surface tension agent with cleansing action similar to soap but active in hard water and non-disturbing to the protective acid balance of the skin. It has been prepared as a prophylactic against athlete's foot and for the treatment of foot discomfort. Supplied in bottles of 4 ounces (114 ml.), 16 ounces (454 ml.), and 80 ounces (2½ litres). (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

the bones, joints, muscles and tendons. Then follow two hundred pages on the surgery of the nervous system by A. Jentzer; this gives rather too full an account of affections of the brain and too little about the peripheral nerves and the sympathetic system, but nevertheless, it is authoritative. In the chapter on the endocrine glands there is a good account of the surgery of diabetes and of the hypoglycæmia caused by islet tumours. The last three chapters deal with subjects which are usually neglected in surgical textbooks—drugs, diet, and physical methods of treatment; all three chapters are rather compressed but it is a refreshing novelty to see them included. The book is well produced and printed and even the small print, of which there is a considerable amount, is easily readable. If the second volume proves as good as the first this textbook will be a great credit to authors, editors and publishers.

Hæmolytic Disease of the Newborn. By M. M. PICKLES, D.M. Oxford: Blackwell Scientific Publications, 1949. Pp. x and 180. Figures 21. Price 15s.

This is quite easily the best account of the subject that has yet been written. Since almost every statement is supported by evidence, the book will be of immense value to those who are trying to put their conception of this disease on a reliable basis. The material on which the account is based is small, it is true, but on the whole one feels that this has been an enormous advantage in giving the writer leisure to confirm every unexpected result until she was sure of it. Only occasionally does one feel that she has been handicapped by having a rather small series of cases: for instance, when she gives the impression, however unwittingly, that since hæmolytic disease of the newborn due to anti-A has not been seen in Oxford, its existence must be seriously doubted. However, rather than find small faults here and there, it is much more important to say as emphatically as possible that here is a really authoritative, clearly written account, which will be of immense help to anyone interested in this disease.

Tuberculous Nursing. By JESSIE G. EYRE, S.R.N., B.T.A. London: H. K. Lewis & Co., Ltd., 1949. Pp. xii and 291. Figures 100. Price 21s.

THE country needs tuberculosis nurses. The author considers that the reluctance of nurses to enter tuberculosis service is due to the fear of infection and "a deeply rooted idea that tuberculosis nursing has 'nothing in it'". The introduction of B.C.G. vaccination, supplementing other preventive measures, will help to

dispel the former. Miss Eyre's book will go a long way towards stimulating an interest in the subject among those who nurse tuberculous patients. The book is attractively and simply written and covers a good deal of ground. It explains what tuberculosis is, how it is recognized, the form it takes, and the complications to which it may give rise. A lack of balance is shown, however, by the inclusion of syphilis of the lung among "the commonest diseases to cause confusion" in the differential diagnosis. The nursing side of treatment is naturally stressed throughout, but collapse therapy is described, as well as measures adopted for the control of extra-pulmonary manifestations such as skeletal and genito-urinary disease. Illustrations are plentiful and of a high standard, and the frontispiece depicts the London Chest Hospital's proposed new building.

An Account of the Schools of Surgery: Royal College of Surgeons, Dublin 1789-1948. By J. D. H. WIDDESS, L.R.C.P.S.S.I. Edinburgh: E. & S. Livingstone Ltd., 1949. Pp. vi and 107. Plates 16. Price 17s. 6d.

MR. WIDDESS gives a most interesting account of the development of surgery and the growth of surgical education in Ireland. The Irish College received its charter sixteen years before the Company of Surgeons was made the Royal College of Surgeons in London, and throughout its history it has taken a prominent part in education. Many well-known names—Abraham Colles, John Cheyne, Dominick Corrigan, Daniel Cunningham, Arthur Jacob, William Stokes, and others equally familiar—appear in these pages. The book, bearing as it does the light touch of an Irish writer describing the colourful history of his fellow countrymen, makes entertaining reading.

The Story of the Johns Hopkins. By BERTRAM M. BERNHEIM, M.D. Kingswood: The World's Work (1913) Ltd., 1949. Pp. xiii and 274. Illustrated. Price 12s. 6d.

AFTER reading this popular history of the famous Johns Hopkins Hospital and Medical School one can fully sympathize with Harvey Cushing's comments on the author's ability "to write English" (p. 108). In spite of this, it is a book to be read. The author is both a graduate and a member of the staff of the Johns Hopkins which he first entered as an undergraduate in 1897, only twelve years after it was founded. He tells his story in colloquial "American" which breaks every law of English grammar but gives a youthful vitality which one traditionally

associates with the early pioneering days of the States. Equally striking is his devastating analysis of his idols, e.g. Osler, and of the institution of which he is a loyal and devoted member. For the author the four "great doctors" of the Johns Hopkins—Osler, Welch, Halstead and Kelly—are among the greatest names in medicine, and yet he does not hesitate to point out their foibles as well as their merits. This is not orthodox history but it makes fascinating reading.

NEW EDITIONS

Nutrition and Diet in Health and Disease, by James S. McLester, M.D. (W. B. Saunders Company, 45s.) has long been recognized as one of the best books on the subject. The fifth edition, which has just been published, well maintains this high reputation. A thorough revision of the whole book has been carried out, particularly in the sections on vitamins and protein, and new food tables have been added. The section on nutrition in disease has also been brought up to date, and now contains a full discussion of high protein diets in liver disease, and the fashionable sodium-free diet in hypertension.

Acute Injuries of the Head, by G. F. Rowbotham, F.R.C.S., in its third edition (E. & S. Livingstone Ltd., 35s.), has been brought up to date on the basis of the many advances in neurosurgery

during the war years. In his preface the author pays warm tribute to Sir Hugh Cairns, Professor Jefferson and Professor Dott for their outstanding services during the war. The new edition is beautifully produced and illustrated.

REWRITING of the chapter on the development of the early ovum, with new illustrations, is one of the features of the tenth edition of *A Synopsis of Obstetrics and Gynaecology*, by Aleck W. Bourne, M.B., B.Ch., F.R.C.S. (John Wright & Sons Ltd., 21s.). Penicillin in gonorrhoea, syphilis, salpingitis, ophthalmia neonatorum, and other conditions is among the new additions.

The Essentials of Chiropody, by Charles A. Pratt, in its second edition (H. K. Lewis & Co. Ltd., 10s. 6d.) has been brought up to date and some illustrations altered. The author, in addition to giving clear, illustrated expositions of the various chiropodial procedures, discusses miscellaneous disorders of the feet, such as athlete's foot, chilblains, sprains, and the like. This is a useful little book for the practitioner.

Training for Childbirth, by Minnie Randell, O.B.E., S.R.N., in its fourth edition (J. & A. Churchill Ltd., 10s. 6d.) contains among new material information on the expression of breast milk, breast feeding and the care of the breasts, and gas and air analgesia. There is a useful chapter on postnatal exercises.

NOTES AND PREPARATIONS

NEW PREPARATIONS

CIMLAC GAUZE is a woven fabric impregnated with a sterilized glyco-gelatin mass containing 5-amino-acridine and hexylresorcinol, both of which are active against gram-positive bacteria and *Ps. pyocaneus*. Rapid control of infection and speedy healing are stated to occur when cimlac gauze is used as a dressing for burns, wounds, boils and carbuncles, varicose ulcers, and impetigo. The gauze is supplied specially packed between two layers of cellulose film to facilitate "non-touch" application. (Calmic Ltd., Crewe Hall, Cheshire.)

DOBAGEN non-staining gentian violet cream (gentian violet and zinc sulphate, each $\frac{1}{2}$ per cent., salicylic acid 2 per cent. approx.) has been prepared for the treatment of epidermophytosis. Advantages claimed for this cream are its non-staining property and quick absorption by the skin. (Forsters [Pharmaceuticals] Ltd., Seaham, Co. Durham.)

LABITON (L.A.B.) kola and vitamin tonic (Vitamin B₁, 7.5 mg.; alcoholic liquid extract of kola nuts, 35 ml.; syrup B.P., 30 ml.; glycerophosphoric acid 20 per cent., 0.25 ml.; flavouring and distilled water to 100 ml.) is stated to act as a stimulant to the central nervous system and as a general tonic in debility and convalescence. (Laboratories for Applied Biology, 6 Percy Street, London, W.1.)

PEDAFORM foot-bath concentrate contains pelarmonic acid, formalin, and a detergent and surface tension agent with cleansing action similar to soap but active in hard water and non-disturbing to the protective acid balance of the skin. It has been prepared as a prophylactic against athlete's foot and for the treatment of foot discomfort. Supplied in bottles of 4 ounces (114 ml.), 16 ounces (454 ml.), and 80 ounces (2½ litres). (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

the bones, joints, muscles and tendons. Then follow two hundred pages on the surgery of the nervous system by A. Jentzer; this gives rather too full an account of affections of the brain and too little about the peripheral nerves and the sympathetic system, but nevertheless, it is authoritative. In the chapter on the endocrine glands there is a good account of the surgery of diabetes and of the hypoglycæmia caused by islet tumours. The last three chapters deal with subjects which are usually neglected in surgical textbooks—drugs, diet, and physical methods of treatment; all three chapters are rather compressed but it is a refreshing novelty to see them included. The book is well produced and printed and even the small print, of which there is a considerable amount, is easily readable. If the second volume proves as good as the first this textbook will be a great credit to authors, editors and publishers.

Hæmolytic Disease of the Newborn. BY M. M. PICKLES, D.M. Oxford: Blackwell Scientific Publications, 1949. Pp. x and 180. Figures 21. Price 15s.

THIS is quite easily the best account of the subject that has yet been written. Since almost every statement is supported by evidence, the book will be of immense value to those who are trying to put their conception of this disease on a reliable basis. The material on which the account is based is small, it is true, but on the whole one feels that this has been an enormous advantage in giving the writer leisure to confirm every unexpected result until she was sure of it. Only occasionally does one feel that she has been handicapped by having a rather small series of cases: for instance, when she gives the impression, however unwittingly, that since hæmolytic disease of the newborn due to anti-A has not been seen in Oxford, its existence must be seriously doubted. However, rather than find small faults here and there, it is much more important to say as emphatically as possible that here is a really authoritative, clearly written account, which will be of immense help to anyone interested in this disease.

Tuberculous Nursing. BY JESSIE G. EYRE, S.R.N., B.T.A. London: H. K. Lewis & Co., Ltd., 1949. Pp. xii and 291. Figures 100. Price 21s.

THE country needs tuberculosis nurses. The author considers that the reluctance of nurses to enter tuberculosis service is due to the fear of infection and "a deeply rooted idea that tuberculosis nursing has 'nothing in it'". The introduction of B.C.G. vaccination, supplementing other preventive measures, will help to

dispel the former. Miss Eyre's book will go a long way towards stimulating an interest in the subject among those who nurse tuberculous patients. The book is attractively and simply written and covers a good deal of ground. It explains what tuberculosis is, how it is recognized, the form it takes, and the complications to which it may give rise. A lack of balance is shown, however, by the inclusion of syphilis of the lung among "the commonest diseases to cause confusion" in the differential diagnosis. The nursing side of treatment is naturally stressed throughout, but collapse therapy is described, as well as measures adopted for the control of extra-pulmonary manifestations such as skeletal and genito-urinary disease. Illustrations are plentiful and of a high standard, and the frontispiece depicts the London Chest Hospital's proposed new building.

An Account of the Schools of Surgery: Royal College of Surgeons, Dublin 1789-1948. BY J. D. H. WIDDESS, L.R.C.P.S.S.I. Edinburgh: E. & S. Livingstone Ltd., 1949. Pp. vi and 107. Plates 16. Price 17s. 6d.

MR. WIDDESS gives a most interesting account of the development of surgery and the growth of surgical education in Ireland. The Irish College received its charter sixteen years before the Company of Surgeons was made the Royal College of Surgeons in London, and throughout its history it has taken a prominent part in education. Many well-known names—Abraham Colles, John Cheyne, Dominick Corrigan, Daniel Cunningham, Arthur Jacob, William Stokes, and others equally familiar—appear in these pages. The book, bearing as it does the light touch of an Irish writer describing the colourful history of his fellow countrymen, makes entertaining reading.

The Story of the Johns Hopkins. BY BERTRAM M. BERNHEIM, M.D. Kingswood: The World's Work (1913) Ltd., 1949. Pp. xiii and 274. Illustrated. Price 12s. 6d.

AFTER reading this popular history of the famous Johns Hopkins Hospital and Medical School one can fully sympathize with Harvey Cushing's comments on the author's ability "to write English" (p. 108). In spite of this, it is a book to be read. The author is both a graduate and a member of the staff of the Johns Hopkins which he first entered as an undergraduate in 1897, only twelve years after it was founded. He tells his story in colloquial "American" which breaks every law of English grammar but gives a youthful vitality which one traditionally

associates with the early pioneering days of the States. Equally striking is his devastating analysis of his idols, e.g. Osler, and of the institution of which he is a loyal and devoted member. For the author the four "great doctors" of the Johns Hopkins—Osler, Welch, Halstead and Kelly—are among the greatest names in medicine, and yet he does not hesitate to point out their foibles as well as their merits. This is not orthodox history but it makes fascinating reading.

NEW EDITIONS

Nutrition and Diet in Health and Disease, by James S. McLester, M.D. (W. B. Saunders Company, 45s.) has long been recognized as one of the best books on the subject. The fifth edition, which has just been published, well maintains this high reputation. A thorough revision of the whole book has been carried out, particularly in the sections on vitamins and protein, and new food tables have been added. The section on nutrition in disease has also been brought up to date, and now contains a full discussion of high protein diets in liver disease, and the fashionable sodium-free diet in hypertension.

Acute Injuries of the Head, by G. F. Rowbotham, F.R.C.S., in its third edition (E. & S. Livingstone Ltd., 35s.), has been brought up to date on the basis of the many advances in neurosurgery

during the war years. In his preface the author pays warm tribute to Sir Hugh Cairns, Professor Jefferson and Professor Dott for their outstanding services during the war. The new edition is beautifully produced and illustrated.

REWRITING of the chapter on the development of the early ovum, with new illustrations, is one of the features of the tenth edition of *A Synopsis of Obstetrics and Gynaecology*, by Aleck W. Bourne, M.B., B.Ch., F.R.C.S. (John Wright & Sons Ltd., 21s.). Penicillin in gonorrhoea, syphilis, salpingitis, ophthalmia neonatorum, and other conditions is among the new additions.

The Essentials of Chiropody, by Charles A. Pratt, in its second edition (H. K. Lewis & Co. Ltd., 10s. 6d.) has been brought up to date and some illustrations altered. The author, in addition to giving clear, illustrated expositions of the various chiropodical procedures, discusses miscellaneous disorders of the feet, such as athlete's foot, chilblains, sprains, and the like. This is a useful little book for the practitioner.

Training for Childbirth, by Minnie Randell, O.B.E., S.R.N., in its fourth edition (J. & A. Churchill Ltd., 10s. 6d.) contains among new material information on the expression of breast milk, breast feeding and the care of the breasts, and gas and air analgesia. There is a useful chapter on postnatal exercises.

NOTES AND PREPARATIONS

NEW PREPARATIONS

CIMLAC GAUZE is a woven fabric impregnated with a sterilized glyco-gelatin mass containing 5-amino-acridine and hexylresorcinol, both of which are active against gram-positive bacteria and *Ps. pyocaneus*. Rapid control of infection and speedy healing are stated to occur when cimlac gauze is used as a dressing for burns, wounds, boils and carbuncles, varicose ulcers, and impetigo. The gauze is supplied specially packed between two layers of cellulose film to facilitate "non-touch" application. (Calmic Ltd., Crewe Hall, Cheshire.)

DOBAGEN non-staining gentian violet cream (gentian violet and zinc sulphate, each $\frac{1}{2}$ per cent., salicylic acid 2 per cent. approx.) has been prepared for the treatment of epidermophytosis. Advantages claimed for this cream are its non-staining property and quick absorption by the skin. (Forsters [Pharmaceuticals] Ltd., Seaham, Co. Durham.)

LABITON (L.A.B.) kola and vitamin tonic (Vitamin B₁, 7.5 mg.; alcoholic liquid extract of kola nuts, 35 ml.; syrup B.P., 30 ml.; glycerophosphoric acid 20 per cent., 0.25 ml.; flavouring and distilled water to 100 ml.) is stated to act as a stimulant to the central nervous system and as a general tonic in debility and convalescence. (Laboratories for Applied Biology, 6 Percy Street, London, W.1.)

PEDAFORM foot-bath concentrate contains pelargonic acid, formalin, and a detergent and surface tension agent with cleansing action similar to soap but active in hard water and non-disturbing to the protective acid balance of the skin. It has been prepared as a prophylactic against athlete's foot and for the treatment of foot discomfort. Supplied in bottles of 4 ounces (114 ml.), 16 ounces (454 ml.), and 80 ounces (2½ litres). (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

ROYAL MEDICAL BENEVOLENT FUND CHRISTMAS GIFTS

LORD WERN-JOHNSTON, President of the Royal Medical Benevolent Fund, writes:—

"Extra comforts at Christmas time are a great help in time of need—the little extra coal, the urgently needed warm clothing, the wherewithal to provide a real Christmas dinner. I appeal to members of the medical profession to bring these comforts to their less fortunate professional brethren, or to their widows and children who are beneficiaries of the Royal Medical Benevolent Fund. Not only will gifts bring them comfort and cheer, but their hearts will be warmed by the kind thought for them. I hope that all, whether subscribers to the Fund or not, will send donations to provide this little extra cheer, and that those who are not subscribers will become regular supporters of the medical profession's own Benevolent Fund".

Donations and subscriptions, marked "Christmas Gifts", should be sent to the Secretary, 1 Balliol House, Manor Fields, Putney, London, S.W.15.

NAPT CHRISTMAS SEALS

THE NAPT Christmas Seals, which again this year are the gift of the Canadian Tuberculosis Association, are now on sale, price 4s. per hundred. Christmas cards, price 6d. each, are also available. The proceeds of the sale are an important item in the budget of the Association for carrying on welfare and educational activities. (NAPT, Tavistock House North, Tavistock Square, London, W.C.1.)



FOOD HYGIENE

Hygienic Food Handling is the title of a manual produced by Messrs. Marks and Spencer for the use of the employees serving in their cafeterias. It should, however, have a much wider circulation, for it presents information of first importance to all concerned with the handling of food in canteens and shops. Especially noteworthy are the sections on refrigeration and on vermin control. The section on legislation should be read in conjunction with the new leaflet issued by I.M. Stationery Office on "Model Byelaws" (Series 1. *Handling, Wrapping and Delivery of Food and Sale of Food in the Open Air*, price 3d.)

OFFICIAL NOTICE

PROPRIETARY infant milk foods and national dried milk, which since April 1948 have been restricted to children up to the age of one year, are now available to children up to two years of

age, as an alternative to liquid milk. To obtain permission for their purchase the child's ration book should be taken to the local food office.

AUREOMYCIN AND CHLOROMYCETIN
To ensure that the available supplies of these drugs are used to the best advantage, the Ministry of Health has arranged to purchase all available supplies and to distribute them through Regional Hospital Board Centres. Hospitals outside the National Health Service will be able to obtain supplies from these centres on payment. On the advice of the Medical Research Council it has been decided for the present to confine the use of these drugs to the treatment of the following conditions.—

Aureomycin: Suspected cases of ornithosis; proved cases of undulant fever (brucellosis); lymphogranuloma inguinale; severe cases of atypical pneumonia in which there is good reason to believe that the cause is a virus.

Chloromycetin: Suspected cases of ornithosis; proved cases of undulant fever (brucellosis); lymphogranuloma inguinale; typhoid fever; paratyphoid fever (severe); salmonella septicaemia.

These categories are under constant review and may be added to from time to time in the light of current expert advice.

PUBLICATIONS

Round the Fountain, an anthology of the best of the humorous articles and verses that have appeared in *St. Bartholomew's Hospital Journal* since 1893, should prove an attractive Christmas gift. (St. Bartholomew's Hospital, London, E.C.1, 4s. 9d. post free.)

The Root and Flower of Vitamin Research is the name of a chart prepared by Crookes Laboratories Ltd., to illustrate the development of the vitamins from their earliest recorded effects to the present day. The chart should be of interest to teachers and lecturers on nutrition and dietetics. (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

Conference on Infertility 1948. This well-edited report of the Fifth Congress, held at Exeter in September 1948, contains much practical material, including tests and modern methods of treatment. (The Family Planning Association, 69 Eecleston Square, London, S.W.1.)

INDEX AND BINDING CASES

The index to Vol. 163 (July-December, 1949) will be forwarded to all subscribers with the January 1950 issue. Binding cases for this and previous volumes are available

inclusive charge of 10s. 6d. per volume; this includes the cost of the binding case and return postage.

The contents of the January 1950 issue, which will contain a symposium on "The Care of the", will be found on page lxx at the end of the section.

1 FEB 1950

THE PRACTITIONER

Edited by

SIR HENEAGE OGILVIE

K.B.E., D.M., M.Ch., F.R.C.S.

WILLIAM A. R. THOMSON, M.D.

ROBERT M. STECHER, M.D., F.A.C.P.



July—December 1949

THE PRACTITIONER
5 BENTINCK STREET, LONDON, W.1

1949

All Rights Reserved

ROYAL MEDICAL BENEVOLENT FUND CHRISTMAS GIFTS

LORD WEBB-JOHNSON, President of the Royal Medical Benevolent Fund, writes:—

"Extra comforts at Christmas time are a great help in time of need—the little extra coal, the urgently needed warm clothing, the wherewithal to provide a real Christmas dinner. I appeal to members of the medical profession to bring these comforts to their less fortunate professional brethren, or to their widows and children who are beneficiaries of the Royal Medical Benevolent Fund. Not only will gifts bring them comfort and cheer, but their hearts will be warmed by the kind thought for them. I hope that all, whether subscribers to the Fund or not, will send donations to provide this little extra cheer, and that those who are not subscribers will become regular supporters of the medical profession's own Benevolent Fund".

Donations and subscriptions, marked "Christmas Gifts", should be sent to the Secretary, 1 Balliol House, Manor Fields, Putney, London, S.W.15.

NAPT CHRISTMAS SEALS

The NAPT Christmas Seals, which again this year are the gift of the Canadian Tuberculosis Association, are now on sale, price 4s. per hundred. Christmas cards, price 6d. each, are also available. The proceeds of the sale are an important item in the budget of the Association for carrying on welfare and educational activities. (NAPT, Tavistock House North, Tavistock Square, London, W.C.1.)



FOOD HYGIENE

Hygienic Food Handling is the title of a manual produced by Messrs. Marks and Spencer for the use of the employees serving in their cafeterias. It should, however, have a much wider circulation, for it presents information of first importance to all concerned with the handling of food in canteens and shops. Especially noteworthy are the sections on refrigeration and on vermin control. The section on legislation should be read in conjunction with the new leaflet issued by H.M. Stationery Office on "Model Byelaws" (Series 1. *Handling, Wrapping and Delivery of Food and Sale of Food in the Open Air*, price 3d.)

OFFICIAL NOTICE

PROPRIETARY infant milk foods and national dried milk, which since April 1948 have been restricted to children up to the age of one year, are now available to children up to two years of

age, as an alternative to liquid milk. To obtain permission for their purchase the child's ration book should be taken to the local food office.

AUREOMYCIN AND CHLOROMYCETIN

To ensure that the available supplies of these drugs are used to the best advantage, the Ministry of Health has arranged to purchase all available supplies and to distribute them through Regional Hospital Board Centres. Hospitals outside the National Health Service will be able to obtain supplies from these centres on payment. On the advice of the Medical Research Council it has been decided for the present to confine the use of these drugs to the treatment of the following conditions:—

Aureomycin: Suspected cases of ornithosis; proved cases of undulant fever (brucellosis); lymphogranuloma inguinale; severe cases of atypical pneumonia in which there is good reason to believe that the cause is a virus.

Chloromycetin: Suspected cases of ornithosis; proved cases of undulant fever (brucellosis); lymphogranuloma inguinale; typhoid fever; paratyphoid fever (severe); salmonella septicaemia.

These categories are under constant review and may be added to from time to time in the light of current expert advice.

PUBLICATIONS

Round the Fountain, an anthology of the best of the humorous articles and verses that have appeared in *St. Bartholomew's Hospital Journal* since 1893, should prove an attractive Christmas gift. (St. Bartholomew's Hospital, London, E.C.1, 4s. 9d. post free.)

The Root and Flower of Vitamin Research is the name of a chart prepared by Crookes Laboratories Ltd., to illustrate the development of the vitamins from their earliest recorded effects to the present day. The chart should be of interest to teachers and lecturers on nutrition and dietetics. (Crookes Laboratories Ltd., Park Royal, London, N.W.10.)

Conference on Infertility 1948. This well-edited report of the Fifth Congress, held at Exeter in September 1948, contains much practical material, including tests and modern methods of treatment. (The Family Planning Association, 69 Eccleston Square, London, S.W.1.)

The index (1949) will be forwarded January 1950 issue. Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 4s. each, post free. The cases are made to hold six copies after the advertisement pages have been removed, they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 10s. 6d. per volume; this includes the cost of the binding case and return postage.

The contents of the January 1950 issue, which will contain a symposium on "The Care of the Newborn", will be found on page lxx at the end of the advertisement section.

	PAGE
HOWELLS, L.: Use and abuse of amphetamine - - - - -	RC 244
HUNTER, W.: Care of the perineum during labour - - - - -	136
INNES, J.: Examination of the blood - - - - -	1
KAUNTZE, R.: Treatment of hypotension - - - - -	NQ 472
—: Procaine lactic acid in osteo- and rheumatoid arthritis— - - - -	NQ 561
KING, D. P.: Examination of the cerebrospinal fluid - - - - -	49
KINYONT, P. D. C.: Treatment of lupus erythematosus - - - - -	NQ 472
LADELL, W. S. S.: Thermal comfort in temperate climates - - - - -	141
LAKE, N. C.: High heels and low heels - - - - -	221
LAW, F. W.: Causation and treatment of detachment of the retina—	187
LEARNMONT, SIR J.: See SLESSOR, A. J. - - - - -	445
LOUDEN, M.: Enemas - - - - -	RC 163
LOUW, J. H.: Natural cure of an acute intussusception, an unusual case history	233
LYALL, A.: Glycosuria - - - - -	25
MACGREGOR, T. N.: Care of the menopausal woman - - - - -	100
MACKENNA, R. M. B.: Advances in the treatment of skin diseases - - - - -	298
—: Bazin's disease - - - - -	NQ 385
MACKENZIE, I.: Modern methods in the treatment of varicose ulcers - - - - -	RC 467
MACEE, A. V.: Note on asthma - - - - -	134
MALKIN, H. JORDAN: Prevention and treatment of prolapse— - - - -	111
MAY, H. B.: Examination of the stools - - - - -	13
MERLEJOHN, A. P.: Advances in nutrition - - - - -	353
MITCHELL-HEGGS, G. B.: Treatment of "athlete's foot" - - - - -	123
MOORE, J.: Pruritus vulvæ - - - - -	106
MUMFORD, P. B.: Barrier creams - - - - -	NQ 560
MURRAY, E. FARQUHAR. Problem of dysmenorrhœa - - - - -	96
NAGLEY, M. M.: Current therapeutics. XXIII.—Para-aminosalicylic acid - - - - -	459
NICHOLLS, M. F.: Advances in urology - - - - -	313
NICOLE, J. E.: Psychiatric rehabilitation in hospital - - - - -	533
NIXON, W. C. W.: Advances in midwifery - - - - -	274
OLIVER, L. C.: Present position of surgery in the treatment of Parkinsonism - - - - -	541
ORAM, S.: Differential diagnosis of palpitation - - - - -	RC 160
PATERSON, A. SPENCER. Refusal of food in childhood - - - - -	NQ 386
PLUNKETT, O. A.: See WILSON, J. W. - - - - -	523
PRICHARD, S.: Cupralen in the treatment of trigeminal neuralgia— - - - -	NQ 82
PRUNTY, F. T. G.: Problem of the etiology of thyrotoxicosis - - - - -	406
PURDIE, A. W.: Toxicæmic albuminuria and pregnancy - - - - -	NQ 82
RICHARDSON, J. S.: Impotence and diabetes - - - - -	NQ 248
RICHES, E. W.: Nocturnal frequency after prostatectomy - - - - -	NQ 471
RUSBY, N. LLOYD. Nursing tuberculosis - - - - -	NQ 472
SELYE, H.: General adaptation syndrome and the diseases of adaptation - - - - -	393
SLESSOR, A. J., and LEARNMONT, SIR J.: Pain in peripheral vascular disease - - - - -	445
SORSBY, A.: Penicillin in ophthalmology - - - - -	194
STALLWORTHY, J.: Obstetric management of a suspected case of erythroblastosis - - - - -	NQ 560
STAMMERS, F. A. R.: Advances in surgery - - - - -	266
STUART, R. D.: Throat swabs - - - - -	17
STUART-HARRIS, C. H.: Modern viewpoint on influenza - - - - -	481
SUGARÉ, H.: Doctor Dover - - - - -	NQ 249
SWYER, G. I. M.: Present clinical status of gonadotrophins - - - - -	428
THOMAS, E. W. PROSSER. Freckles - - - - -	63
THOMAS, J. W. TUDOR. Ophthalmic emergencies - - - - -	207
THOMSON, W. A. R.: British Pharmaceutical Codex 1949 - - - - -	544
THORN, G. W., and BAYLES, T. B.: Current therapeutics XXII.—Pituitary adrenal function and rheumatic disease - - - - -	365
TOUGH, J. S.: Treatment of burns - - - - -	RC 469
WHITBY, SIR LIONEL. Advances in the treatment of blood diseases - - - - -	290
WHITTAKER, H.: Treatment of diabetes mellitus in infancy and childhood - - - - -	413
WHITTLE, C. H.: Investigation of tinea infestations - - - - -	31
WILES, P.: Advances in orthopædics - - - - -	305
WILKIE, J. L.: Modern treatment of squint - - - - -	200
WILKINSON, J. F.: Current therapeutics. XXIV.—Hæmostatics - - - - -	548
WILLIAMSON, B.: Constipation in infancy and childhood - - - - -	RC 242
WILSON, C.: Advances in medicine - - - - -	257
WILSON, J. W., and PLUNKETT, O. A.: Practical medical mycology— - - - -	523
WOOLMER, R.: Advances in anæsthesia - - - - -	320
WOOTTON, I. D. P.: Estimation of hæmoglobin - - - - -	RC 77
YOUNG, J.: Present status of treatment of cancer of the uterine cervix and body	89

GENERAL INDEX

TO VOLUME 163

SYMPOSIA

PAGE

1- 53

Symposium on clinical pathology	-	-	-	-	-	-	-
— on gynaecology	-	-	-	-	-	-	89-1
— on diseases of the eye	-	-	-	-	-	-	-
— on advances in treatment	-	-	-	-	-	-	-
— on endocrinology	-	-	-	-	-	-	-
— on respiratory diseases	-	-	-	-	-	-	-

INDEX TO NAMES OF AUTHORS

Abbreviations: *abs*—Abstract; *NQ*—Note and Query; *RC*—Revision

ABRAHAMS, SIR ADOLPHE: Winter resort for vasomotor disturbance	-	-	-	-	-	-	-
AMOR, A. J.: Advances in industrial medicine	-	-	-	-	-	-	-
ANDERSON, T.: Use and abuse of penicillin in respiratory infections	-	-	-	-	-	-	-
ARCHER, H. E.: Tests of renal function	-	-	-	-	-	-	-
ARNOTT, W. MELVILLE: Current therapeutics. XIX.—Sympathomimetic action and its antagonism	-	-	-	-	-	-	-
BALLANTYNE, A. J.: Eye in general medicine	-	-	-	-	-	-	-
BAMFORTH J.: Blood agglutination tests	-	-	-	-	-	-	-
BARBER, H. W.: Allergic dermatitis of the eyelids	-	-	-	-	-	-	-
BAYLES, T. B.: See THORN, G. W.	-	-	-	-	-	-	-
BEATTIE, J.: Current therapeutics. XXI.—Protein hydrolysates	-	-	-	-	-	-	-
BERRY, W. T. C.: Administration of vitamins to members of police force	-	-	-	-	-	-	-
BETTLEY, F. R.: Hirsuties of the upper lip	-	-	-	-	-	-	-
BIRCH, C. A.: Primary atypical pneumonia	-	-	-	-	-	-	-
BISHOP, P. M. F.: Postponement of menstrual bleeding	-	-	-	-	-	-	-
—: Hormone implantation therapy	-	-	-	-	-	-	-
BONHAM-CARTER, R. E.: Sedation for infants	-	-	-	-	-	-	-
—: Acute respiratory infections in infants	-	-	-	-	-	-	-
BOWES, K.: Present status of dilatation and curettage	-	-	-	-	-	-	-
CADE, SIR STANFORD: Advances in the treatment of cancer	-	-	-	-	-	-	-
CAMPBELL, M.: Cardiac failure under chloroform anaesthesia	-	-	-	-	-	-	-
CHAMBERS, J. W.: Use and abuse of calcium	-	-	-	-	-	-	-
CLARKE, C. A.: Asthma in childhood: experiences in a Liverpool play	-	-	-	-	-	-	-
—: Carbon dioxide in asthma	-	-	-	-	-	-	-
CLAYTON, S. G.: Treatment of threatened abortion	-	-	-	-	-	-	-
CRUICKSHANK, D. BARRON: Bacteriological investigation of pulmonary tuberculosis from the aspect of clinical pathology	-	-	-	-	-	-	-
DANIELS, M.: Advances in the treatment of tuberculosis	-	-	-	-	-	-	-
DAVIDSON, M.: Diagnosis and treatment of empyema	-	-	-	-	-	-	-
DODDS, E. C.: Problem of production of steroid hormones	-	-	-	-	-	-	-
DODDS, G. H.: Early diagnosis of carcinoma of the uterus	-	-	-	-	-	-	-
DOWLING, G. B.: Erythrocytosis erurum	-	-	-	-	-	-	-
DUKES, C. E.: Biopsy	-	-	-	-	-	-	-
DUNLOP, D. M.: Stimulant action of dexedrine	-	-	-	-	-	-	-
EVANS, R. G.: Cardiospasm	-	-	-	-	-	-	-
FAIRBROTHER, R. W.: Blood cultures	-	-	-	-	-	-	-
FERGUSON, J. D.: Acute retention	-	-	-	-	-	-	-
GAISFORD, W.: Advances in paediatrics	-	-	-	-	-	-	-
GEIKIE-COBB, I.: Bentinck Street and Marylebone, a historical causerie	-	-	-	-	-	-	-
GOOD, M. G.: Painful feet	-	-	-	-	-	-	-
GUNN, W.: Advances in the treatment of acute infectious diseases	-	-	-	-	-	-	-
HADLEY, G. D.: Flatulence and the use of carminatives	-	-	-	-	-	-	-
HANDLEY, R. S.: Treatment of boils	-	-	-	-	-	-	-
HARGREAVES, W. H.: Current therapeutics. XX.—Aureomycin and chlormycesetin	-	-	-	-	-	-	-
HARTRIDGE, H.: Colour blindness in the light of recent theories of colour vision	-	-	-	-	-	-	-
HARTSILVER, J.: Clinical influenza	-	-	-	-	-	-	-
HAXTON, H. A.: Chemical sympathectomy	-	-	-	-	-	-	-
HELLIER, F. F.: Thorium-X treatment in tinea unguium	-	-	-	-	-	-	-
HENDERSON, J. L.: Treatment of ulceration of the mouth in children	-	-	-	-	-	-	-
HILL, I. G. W.: Oxygen therapy	-	-	-	-	-	-	-
HIND, A. W.: Trilene anaesthesia	-	-	-	-	-	-	-
HODGSON, G.: Care of the scalp and hair	-	-	-	-	-	-	-
—: Rapid loss of hair in elderly patient	-	-	-	-	-	-	-
HOWELL, TREVOR H.: A.B.C. of geriatrics	-	-	-	-	-	-	-

	PAGE
Athlete's foot, differential diagnosis of - - - - -	123
—, non-fungous origin, treatment of - - - - -	128
—, treatment of - - - - -	125
Atropine, use of, in eye injuries, caution in - - - - -	209
Aureomycin in atypical pneumonia - - - - -	286, 350
— <i>B. abortus</i> infection - - - - -	262, 286, 349
— bacterial infections - - - - -	155
— pneumonia - - - - -	262, 350
— primary atypical pneumonia - - - - -	350, 500
— rickettsial and virus diseases - - - - -	152
— spirochætal infections - - - - -	158
— typhoid fever - - - - -	349
— whooping-cough - - - - -	508
—, range of activity - - - - -	151
Bacteriæmia - - - - -	33
B.A.L. in pink disease - - - - -	289
Baldness, premature - - - - -	217
Banti's syndrome, treatment of, surgical - - - - -	271
Barrier creams - - - - -	NQ 560
Batchelor's hip operation - - - - -	306
Bazin's disease - - - - -	NQ 385
B.C.G. vaccination - - - - -	265, 283, 347
Bee stings, treatment of - - - - -	abs 252
Bentinck Street, history of - - - - -	54
Benzedrine, action of - - - - -	74
Beryllium, effects of, on human body - - - - -	361
Biopsy, aspiration - - - - -	8
—, bronchial - - - - -	11
— during radiation treatment of cancer of uterus - - - - -	94
—, endometrial - - - - -	9, 118
— in bladder diseases - - - - -	10
— liver diseases - - - - -	11
— rectal diseases - - - - -	9
— of lymph nodes - - - - -	11
—, serial, in control of radiation and hormone therapy - - - - -	11
—, surgical, risks of - - - - -	7
—, testicular - - - - -	11
Bis-dehydro-choisynolic acid, formula of - - - - -	426
Bladder, carcinoma of, treatment of - - - - -	319
—, paraplegic, care of - - - - -	317
B.L.B. mask for oxygen administration - - - - -	518
Blepharitis, treatment of, penicillin - - - - -	197
Blindness, causes of - - - - -	174, 175
Blood agglutination tests - - - - -	36
— alkali reserve, normal and in impaired kidney function - - - - -	47
— cholesterol, normal and in impaired kidney function - - - - -	48
— coagulation, mechanism of - - - - -	548
— creatinine, normal - - - - -	44
— cultures - - - - -	33
—, examination of - - - - -	1
— count, normal - - - - -	2
—, diseases of, treatment of, advances in - - - - -	290
— film, stained, preparation and examination of - - - - -	1
— hæmoglobin, estimation of, - - - - -	1, 3, RC 77
— non-protein nitrogen, normal - - - - -	44
— platelets, examination of - - - - -	3
— pressure, diet in relation to - - - - -	356
—, high, at menopause, treatment of - - - - -	105
— sugar curves, estimation of, in glycosuria, importance in diagnosis - - - - -	27, 29
— urea, normal - - - - -	44
Body temperature, nervous control of - - - - -	143
—, vascular system in relation to - - - - -	142
Boils, treatment of - - - - -	RC 162
Bone grafting, cancellous bone - - - - -	306
— marrow, examination of - - - - -	5
Breast, cancer of, treatment of, hormones - - - - -	343, abs 387
—, —, —, radio-surgical - - - - -	341
Breathing exercises, pre- and post-operative, value of - - - - -	266
British Pharmaceutical Codex 1949 - - - - -	544

	PAGE
Athlete's foot, differential diagnosis of - - - - -	123
—, non-fungous origin, treatment of - - - - -	128
—, treatment of - - - - -	125
Atropine, use of, in eye injuries, caution in - - - - -	209
Aureomycin in atypical pneumonia - - - - -	286, 350
— <i>B. abortus</i> infection - - - - -	262, 286, 349
— bacterial infections - - - - -	155
— pneumonia - - - - -	262, 350
— primary atypical pneumonia - - - - -	350, 500
— rickettsial and virus diseases - - - - -	152
— spirochætal infections - - - - -	158
— typhoid fever - - - - -	349
— whooping-cough - - - - -	508
—, range of activity - - - - -	151
Bacteraemia - - - - -	33
B.A.L. in pink disease - - - - -	289
Baldness, premature - - - - -	217
Banti's syndrome, treatment of, surgical - - - - -	271
Barrier creams - - - - -	NQ 560
Batchelor's hip operation - - - - -	306
Bazin's disease - - - - -	NQ 385
B.C.G. vaccination - - - - -	265, 283, 347
Bee stings, treatment of - - - - -	abs 252
Bentinck Street, history of - - - - -	54
Benzedrine, action of - - - - -	74
Beryllium, effects of, on human body - - - - -	361
Biopsy, aspiration - - - - -	8
—, bronchial - - - - -	11
— during radiation treatment of cancer of uterus - - - - -	94
—, endometrial - - - - -	9, 118
— in bladder diseases - - - - -	10
— liver diseases - - - - -	11
— rectal diseases - - - - -	9
— of lymph nodes - - - - -	11
—, serial, in control of radiation and hormone therapy - - - - -	11
—, surgical, risks of - - - - -	7
—, testicular - - - - -	11
<i>Bis</i> -dehydro-doisylnolic acid, formula of - - - - -	426
Bladder, carcinoma of, treatment of - - - - -	319
—, paraplegic, care of - - - - -	317
B.L.B. mask for oxygen administration - - - - -	518
Blepharitis, treatment of, penicillin - - - - -	197
Blindness, causes of - - - - -	174, 175
Blood agglutination tests - - - - -	36
— alkali reserve, normal and in impaired kidney function - - - - -	47
— cholesterol, normal and in impaired kidney function - - - - -	48
— coagulation, mechanism of - - - - -	548
— creatinine, normal - - - - -	44
— cultures - - - - -	33
—, examination of - - - - -	1
— count, normal - - - - -	2
—, diseases of, treatment of, advances in - - - - -	290
— film, stained, preparation and examination of - - - - -	1
— hæmoglobin, estimation of, - - - - -	1, 3, RC 77
— non-protein nitrogen, normal - - - - -	44
— platelets, examination of - - - - -	3
— pressure, diet in relation to - - - - -	356
—, high, at menopause, treatment of - - - - -	105
— sugar curves, estimation of, in glycosuria, importance in diagnosis - - - - -	27, 29
— urea, normal - - - - -	44
Body temperature, nervous control of - - - - -	143
—, vascular system in relation to - - - - -	142
Boils, treatment of - - - - -	RC 162
Bone grafting, cancellous bone - - - - -	306
— marrow, examination of - - - - -	5
Breast, cancer of, treatment of, hormones - - - - -	343, abs 387
—, —, —, radio-surgical - - - - -	341
Breathing exercises, pre- and post-operative, value of - - - - -	266
British Pharmaceutical Codex 1949 - - - - -	544

	PAGE
Bronchiolitis in infants, treatment of	504
Bronchitis, capillary, treatment of, oxygen	520
— in infants, diagnosis and treatment of	503
Burns, treatment of	RC 469
Caleiferol in lupus vulgaris	335
— in skin tuberculosis	299
— tuberculous cervical adenitis	335
Calcium alginate, hæmostatic action of	553
—, dietary requirements of	RC 78
— preparations and methods of administration	RC 79
—, use and abuse of	RC 78
Callosities, treatment of	228
Calorie deficiency, signs and symptoms of	355
Cancer, treatment of, advances in	337
Carbon monoxide poisoning, treatment of, oxygen	521
Carcinogenesis, chemical	361
Cardiospasm, diagnosis and treatment of	RC 246
—, treatment of, Heller operation	269
Caries, dental, prevention of, fluorine	abs 388
Carriers, typhoid, agglutination reactions in	39
Cataract, congenital, etiology of, maternal rubella	177
Causalgia, sympathetic block in	325
Cerebral cortex, regional excision of, in Parkinsonism	542
Cerebrospinal fluid, bacteriology of	51
—, chlorides in	52
—, colour, protein and cell content of	49, 50
—, examination of	49
—, —, in streptomycin therapy of tuberculous meningitis	53
—, glucose in	53
—, withdrawal of, technique of	49
Chemical industry, safety rules in	364
Chest complications, post-operative	266
Chloromycetin in acute-laryngotracheo-bronchitis in infants—	505
— bacterial infections	155
— primary atypical pneumonia	501
— rickettsial and virus diseases	152
— scrub-typhus	262
— spirochætal infections	158
— typhoid fever	263, 286, 348, abs 561
— whooping-cough	508
Cholesterol, formula of	423
Chondromalacia patellæ, symptoms and treatment of	309
Claudication, intermittent, pain in	445
Climates, temperate, thermal comfort in	141
Cœliac disease, treatment of	287
Cold, common, treatment of	351
—, protection against, outdoor clothing for	147
Colitis, ulcerative, treatment of, ileostomy and Rutzen bag	271
Colon, cancer of, treatment of	338
Colorimeters, photo-electric, for hæmoglobin estimation	RC 78
Colour blindness, diagnosis of	182, 185
— vision, polychromatic	184
—, trichromatic	182
Coma, diabetic, and insulin, in children	417, 418
Compound E, formula of	425
— in rheumatoid arthritis	258, 371
Concentration test of renal function	47
Conjunctiva, wounds of	209
Conjunctivitis, treatment of, penicillin	197
Constipation in infancy and childhood	RC 242
Contact lenses	abs 250
Cordotomy in Parkinsonism	542
Cornea, ulcer of, infected, with hypopyon, treatment of, penicillin	198
Coronary occlusion, massive, treatment of, oxygen	521
Corticosterone, formula of	421
Cortisone in rheumatoid arthritis	258
Coryza in infants	502
Cross-infection, prevention of	345
Curare, use of as muscle relaxant	320

	PAGE
Cyclobutane - - - - -	324
Dacrocystitis, acute, treatment of, penicillin - - - - -	199
Dandruff, etiology and treatment of - - - - -	218, 300
Decamethonium iodide as anæsthetic - - - - -	abs 83
----- as muscle relaxant - - - - -	320
Dehydroandrosterone, formula of - - - - -	423
Dehydrocorticosterone, formula of - - - - -	424
Dehydroergocornine, use of as sympathicolytic agent - - - - -	76
Dendritic ulcer, treatment of, local urea - - - - -	abs 562
Deoxycholic acid, formula of - - - - -	425
Deoxycorticosterone acetate implantation therapy, indications for - - - - -	444
Dermatitis, impetiginized, treatment of - - - - -	300
Dermatology, use of oral bismuth in - - - - -	abs 475
Desoxycorticosterone, formula of - - - - -	424
Dexedrine, stimulant action of - - - - -	NQ 166
Dextran plasma substitute - - - - -	264
Dhobie's itch - - - - -	30
Diabetes mellitus and impotence - - - - -	NQ 248
-----, diagnosis of - - - - -	26
-----, eyes in - - - - -	176, 179, 181
----- in infancy and childhood, treatment of - - - - -	413
-----, pregnancy in - - - - -	277
-----, treatment of, significance of recurrent glycosuria in - - - - -	28
Diarrhœa as complication of coryza in infancy - - - - -	503
----- due to hydrolysate feeding, treatment of - - - - -	237
Diathermy in treatment of detachment of retina - - - - -	191
Dienœstrol, formula of - - - - -	425
Diet in diabetes mellitus in infancy and childhood - - - - -	423
----- relation to infection - - - - -	356
Diethylstilbœstrol in mumps - - - - -	349
Dihydrostreptomycin, use of - - - - -	285
Dilatation in spasmodic dysmenorrhœa - - - - -	97, 120
Dilution test of renal function - - - - -	46
Dimethyl-ethyl-allenolic acid, formula of - - - - -	426
Diphtheria carriers, treatment of - - - - -	283
----- immunization - - - - -	283, 346
-----, laryngeal, treatment of - - - - -	512
Doisynolic acid, formula of - - - - -	426
Dolophine - - - - -	324
Dover, Doctor - - - - -	NQ 249
Dysentery, bacillary, agglutination tests in - - - - -	41
Dysmenorrhœa, congestive, etiology and treatment of - - - - -	98
-----, spasmodic, etiology and treatment of - - - - -	96, 120
Eales's disease, intra-ocular hæmorrhage in - - - - -	174, 212
Ear, middle, tuberculosis of - - - - -	24
Eczema of vulva - - - - -	107
Embolism, pulmonary, massive, treatment of, oxygen - - - - -	521
-----, postoperative, prevention and treatment of - - - - -	267
Emphysema, obstructive, in infants, etiology and treatment of - - - - -	507
-----, treatment of, oxygen - - - - -	520
Empyema, acute - - - - -	489
-----, chronic - - - - -	494
----- in infants - - - - -	507
-----, secondarily infected, bacteriological examination in - - - - -	24
-----, syn-pneumonic - - - - -	514
-----, tuberculous - - - - -	495
Endocarditis, bacterial, blood cultures in - - - - -	34
-----, infective, treatment of, combined penicillin and vitamin C - - - - -	abs 85
Endocrine organs, interrelations of, functional - - - - -	396
Endometriosis in etiology of congestive dysmenorrhœa - - - - -	99
Enemas, indications for and choice of - - - - -	RC 163
Enteric fever, agglutination reactions of - - - - -	37
-----, blood cultures in - - - - -	34
Ephedrine, action of - - - - -	73
Epiglottitis, acute, epidemic, in infants - - - - -	504
Epilepsy, minor, treatment of, tridione - - - - -	abs 389
-----, treatment of, papaverine - - - - -	abs 167
Epinephrine in treatment of rheumatoid arthritis - - - - -	373
----- stimulation of anterior pituitary-adrenal cortical system - - - - -	369

	PAGE
Epinine, action of - - - - -	73
Episiotomy, indications for, technique of - - - - -	137, 138
Erythema nodosum, etiology of - - - - -	abs 389
Erythroblastosis foetalis, obstetric management of suspected case of - - - - -	NQ 560
—, treatment of - - - - -	293
Erythrocyanosis crurum, treatment of - - - - -	NQ 81
Erythrocytes, examination of - - - - -	2
Erythroidin, use of, as muscle relaxant - - - - -	321
Ethinyl œstradiol, formula of - - - - -	426
Eye, burns of, varieties and treatment of - - - - -	209
—, foreign bodies in - - - - -	207
— in general medicine - - - - -	173
—, infections of, diagnosis of - - - - -	194
—, —, —, treatment of, nicotinic acid and its derivatives - - - - -	abs 167
—, pain in, acute - - - - -	212
Eyeball, wounds of - - - - -	208
Eyelids, dermatitis of, allergic - - - - -	NQ 165
Fæces, examination of - - - - -	16
Fallot's tetralogy, treatment of - - - - -	273
Fat balance test - - - - -	14
Favus, etiology of - - - - -	32
Fect, effect of high heels on - - - - -	222
—, painful, etiology of - - - - -	229
Ferrivenin in iron deficiency anæmias - - - - -	291
Fibrin foam, hæmostatic action of - - - - -	552
Fibrinogen, formation and action of - - - - -	551
Fingers, clubbing of - - - - -	168
Flatulence, use of carminatives in - - - - -	RC 381
Flaxcdil - - - - -	320 abs 563
Fluorescent lighting, hazards of - - - - -	361 abs 476
Folic acid antagonists in treatment of cancer - - - - -	343
— in anæmias - - - - -	291
Folliculitis, treatment of - - - - -	300
Food, refusal of in childhood - - - - -	NQ 386
Foot arthrodesis, use of cancellous grafts - - - - -	308
—, fungus infection of, treatment of - - - - -	125
—, myalgia of - - - - -	229
Fothergill or Manchester operation for prolapse - - - - -	117
Fractures, ununited, use of cancellous grafts - - - - -	308
Freckles, differential diagnosis and treatment of - - - - -	64
Fungi, laboratory methods of examination - - - - -	523, 529, 530
Fungicides, application of - - - - -	126
Fungous infections, treatment of - - - - -	300
Gangrene, pain in - - - - -	449
Gastric lavage in diagnosis of tuberculosis - - - - -	22
Gastro-enteritis in infancy, etiology and treatment of - - - - -	286, 287, 349
Gelatin sponge, hæmostatic action of - - - - -	553
Geriatrics, special problems of - - - - -	67
Glands, tuberculous, diagnosis of - - - - -	23
Glandular fever, Paul-Bunnell test for - - - - -	36
Glaucoma, acute, diagnosis and treatment of - - - - -	211
Glycosuria - - - - -	25
Goitre, puberty - - - - -	407
—, treatment of, bismuth - - - - -	abs 251
Gonadotrophins, clinical status of - - - - -	428
Gonin's operation for detachment of retina - - - - -	191
Gonorrhœa, prevention of, penicillin tablets - - - - -	abs 387
Guist-Lindner's operation for detachment of retina - - - - -	191
Gynæcomastia and cirrhosis of liver - - - - -	abs 252
Hæmagglutination - - - - -	36
Hæmorrhage, accidental, in pregnancy - - - - -	276
—, antepartum, treatment of - - - - -	276
—, intra-ocular, recurrent, in Eales's disease - - - - -	174, 212
—, postpartum, etiology and prophylaxis of - - - - -	280
—, uterine, diagnosis of, dilatation and curettage - - - - -	119, 120
Hæmorrhagic diseases, blood examination in - - - - -	5
Hæmostatics - - - - -	548, 549, 551
—, snake venoms - - - - -	553
Hair, care of - - - - -	213

	PAGE
Khellin, coronary vasodilator action of	abs 84
Kidney diseases, treatment of, advances in	264, 564
—, effect of mineralo-corticoids on	397
—, endocrine	399, 400, 401
—, tuberculosis of, diagnosis of	23
Knee arthrodesis, use of cancellous grafts	307
Kraurosis vulvæ at menopause, treatment of	104, 107, 110
Labour, care of perineum during	136
Lactosuria in pregnancy and lactation	25
Lange's colloidal gold test	52
Laryngeal swabs in diagnosis of tuberculosis	22
Laryngotracheo-bronchitis, acute, in infants, treatment of	504
Larynx, tuberculosis of, treatment of, streptomycin	333
Lavage in diagnosis of tuberculosis	22
Lens, wounds of	208
Leucocytes, disorders affecting	4
—, examination of	2
Leucoplakia vulvæ	108
— at menopause, treatment of	105
—, treatment of	110
Leukæmia, acute	294
—, chronic	294
—, inhibited by folic acid	288
Lice, head, treatment of, gammexane	abs 475
Lip, upper, hirsuties of	NQ 559
Liver, cirrhosis of, gynæcomastia complicating	abs 252
— sympathin	73
Lung, cancer of, treatment of	338
—, collapse of, in respiratory infections in infants, treatment of	506
— complications of influenza	484
—, fibrosis of, treatment of, oxygen	520
Lupus erythematosus disseminata, treatment of, ACTH	376
—, treatment of	NQ 472
— vulgaris, treatment of, calciferol	335
Macula, hæmorrhage at, loss of vision in	212
Manchester or Fothergill operation for prolapse	117
Marylbone, history of	54
Measles immunization	348
Medicine, advances in	257
—, African, native	235
—, general, eye symptoms in	173
—, industrial, advances in	360
—, —, legislation in	363
Meningitis, examination of cerebrospinal fluid in	51
—, diagnosis of	24
—, treatment of	286
—, —, streptomycin	331
Meningococcal infections, blood cultures in	34
Menopause, syndrome of, treatment of	100
Menstrual bleeding, postponement of	NQ 248
Menstruation and thyrotoxicosis	407
Metabolism, carbohydrate, and skin diseases	301
Metatarsalgia, anterior	311
—, Morton's, symptoms and treatment of	311
Metatarsals, spreading and splaying of, treatment of	228
Methadon	324
Miadone	324
Midwifery, advances in	274
Mortality, infant, statistics of	274, 282
—, maternal, statistics of	274
Morton's metatarsalgia, symptoms and treatment of	311
Mouth ulceration of, in children, treatment of	NQ 166
Mumps immunization	349
— orchitis, treatment of, diethylstilbæstrol	abs 250
—, treatment of	349
Muscle relaxants, use of	320
Myalgia of foot, etiology of	229
—, treatment of	231
Mvanesin, use of, as muscle relaxant	320

	PAGE
Mycology, medical	523
Mycoses, superficial, microscopic features of fungi responsible for	529, 530
Myeloma, treatment of	296
Nails, ringworm of	33
Nephritis, etiology of	403
Nephrosclerosis, etiology of	397, 400
Neuralgia, trigeminal, treatment of, cupralein	NQ 82
Neurectomy, presacral, in spasmodic dysmenorrhœa	97
Neuritis, ischæmic, pain in	448
——, retrobulbar optic, vision in	174, 212
Neurodermatoses	303
Newborn, care of	283
——, hæmolytic disease of, treatment of	282
——, skin of, care of	abs 169
Nipple, eczema of, treatment of, œstrogens	abs 167
Nitrogen mustard in cancer	342
—— in chronic leukæmia	296
Nonne-Apelt test	50, 52
Nor-adrenaline	73

NOTES AND PREPARATIONS:

Anacodin, 392; Analos, 392; Antustin cream and ointment, 480; Aureomycin, 480, 568; British Rheumatic Association, 256; Chloromycetin, 568; Ciba Foundation, 172; Cimlac gauze, 567; Cresatin, 256; Digophyllin A.F.D., 172; Disecron, 256; Dobagen, 567; Fel-evac, 172; Flaxedil, 172; Gelatin sponge A & H., 88; Glycurrant cough linctus, 392; Injection solution BAL, 480; Iquimol, 256; Labiton (L.A.B.), 567; Lachesine, 88; Lactalumina compound, 480; Linguets of percarton, 88; Medical Directory, 172; Medical films, 88, 256, 480; Methionine B.D.H., 256; Mycal pessaries, 172; NAPT Christmas seals, 568; NAPT locum register, 88; Neo-Selaron, 88; Optalidon, 480; Pedaform, 567; Penicillin cryptic powder, 88; Rose-hip L.B.W., 88; Royal Medical Benevolent Fund, 392; Royal Medical Benevolent Fund Christmas gifts, 568; Royal Society of Medicine, 172; Streptomycin, 392; Televised eye operations at St. Thomas's, 256.	
Nutrition, advances in	353
Obesity, treatment of	abs 83
Obliterative arteritis, pain in	445
Œdema, pulmonary, treatment of, oxygen	520
Œsophagus, cancer of, treatment of	269, 338
Œstradiol, formula of	420
Œstrogen implantation therapy, indications for	443
—— therapy at menopause, dosage and methods of administration	102
—— of acne vulgaris	301
—— cancer of breast	344
—— cancer of prostate	343
—— kraurosis vulvæ	110
Œstrogens, synthetic	425
Œstrone, formula of	420
Old age, special problems of	67
Onychomycosis	33
Ophthalmia neonatorum, treatment of, penicillin	196
Ophthalmic emergencies	207
Orbit, fractures of	209
Oro-pharynx, tuberculous ulcers of, treatment of, streptomycin	333
Orthopædics, advances in	305
Orthoptics in treatment of squint	201
Osteomyelitis, acute, treatment of	310
Otitis media in infants, treatment of	503
Ovulation, induction of, by gonadotrophins	435
Oxidized cellulose, hæmostatic action of	551
Oxygen therapy	517
Pædiatrics, advances in	282
Pain in peripheral vascular disease	445
——, postoperative, sympathetic block in	326
Palpitation, differential diagnosis and treatment of	RC 160
Pancreas, cystic fibrosis of, treatment of	287, 288
Para-aminosalicylic acid	460
—— in extrathoracic tuberculosis	286
—— in tuberculosis	334, 460
Paratyphoid fever, agglutination reactions in	37
Paredrine, action of	73
Parkinsonism, treatment of, surgical, procedures and results	541
—— trihexyphenidyl (artane)	abs 473
Paronychia, chronic	33
Patent ductus arteriosus, treatment of	273

	PAGE
Khellin, coronary vasodilator action of	abs 84
Kidney diseases, treatment of, advances in	264, 564
—, effect of mineralo-corticoids on	397
—, endocrine	399, 400, 401
—, tuberculous of, diagnosis of	23
Knee arthrodesis, use of cancellous grafts	307
Kraurosis vulvæ at menopause, treatment of	104, 107, 110
Labour, care of perineum during	136
Lactosuria in pregnancy and lactation	25
Lange's colloidal gold test	52
Laryngeal swabs in diagnosis of tuberculosis	22
Laryngotracheo-bronchitis, acute, in infants, treatment of	504
Larynx, tuberculosis of, treatment of, streptomycin	333
Lavage in diagnosis of tuberculosis	22
Lens, wounds of	208
Leucocytes, disorders affecting	4
—, examination of	2
Leucoplakia vulvæ	108
— at menopause, treatment of	105
—, treatment of	110
Leukæmia, acute	294
—, chronic	294
—, inhibited by folic acid	288
Lice, head, treatment of, gammexane	abs 475
Lip, upper, hirsuties of	NQ 559
Liver, cirrhosis of, gynæcomastia complicating	abs 252
— sympathin	73
Lung, cancer of, treatment of	338
—, collapse of, in respiratory infections in infants, treatment of	506
—, complications of influenza	484
—, fibrosis of, treatment of, oxygen	520
Lupus erythematosus disseminata, treatment of, ACTH	376
—, treatment of	NQ 472
— vulgaris, treatment of, calciferol	335
Macula, hæmorrhage at, loss of vision in	212
Manchester or Fothergill operation for prolapse	117
Marylebone, history of	54
Measles immunization	348
Medicine, advances in	257
—, African, native	235
—, general, eye symptoms in	173
—, industrial, advances in	360
—, —, legislation in	363
Meningitis, examination of cerebrospinal fluid in	51
—, diagnosis of	24
—, treatment of	286
—, —, streptomycin	331
Meningococcal infections, blood cultures in	34
Menopause, syndrome of, treatment of	100
Menstrual bleeding, postponement of	NQ 248
Menstruation and thyrotoxicosis	407
Metabolism, carbohydrate, and skin diseases	301
Metatarsalgia, anterior	311
—, Morton's, symptoms and treatment of	311
Metatarsals, spreading and splaying of, treatment of	228
Metadon	324
Miadone	324
Midwifery, advances in	274
Mortality, infant, statistics of	274, 282
—, maternal, statistics of	274
Morton's metatarsalgia, symptoms and treatment of	311
Mouth ulceration of, in children, treatment of	NQ 166
Mumps immunization	349
— orchitis, treatment of, diethylstilbæstrol	abs 250
—, treatment of	349
Muscle relaxants, use of	320
Myalgia of foot, etiology of	229
—, —, treatment of	231
Myanesin, use of, as muscle relaxant	320

	PAGE
Pruritus, treatment of, papaverine - - - - -	abs 253
— vulvæ, etiology, pathology and treatment of - - - - -	106, 109
—, —, —, sodium propionate - - - - -	abs 475
Psoriasis, treatment of - - - - -	300
—, —, —, calciferol - - - - -	abs 85
Psychiatry, rehabilitation in - - - - -	533
Psychoneuroses, pruritus vulvæ in - - - - -	109
Psychosis at menopause, treatment of - - - - -	105
Pterine in leukaemia - - - - -	296
Puberty, delayed, treatment of, gonadotrophins - - - - -	434, 435
Pulmonary lavage in diagnosis of tuberculosis - - - - -	22
Pyogenic infections, blood cultures in - - - - -	34
Quinine blindness - - - - -	175
—, use of, as muscle relaxant - - - - -	321
Radiation sickness, treatment of, dramamine - - - - -	abs 562
Radioactive iodine in diagnosis of thyroid dysfunction - - - - -	264
— phosphorus and carbon in treatment of cancer - - - - -	340
Radiotherapy and surgery in cancer - - - - -	339, 341
Radium treatment of cancer of uterus at Radiumhemmet, Stockholm - - - - -	95
Read-Millen operation for prolapse - - - - -	117
Rectum, cancer of, treatment of - - - - -	338
Rehabilitation, postpartum - - - - -	281
—, psychiatric, in hospital - - - - -	533
Renal function tests, choice of - - - - -	43
— threshold, low, in diabetic children - - - - -	417
Respiratory infections, acute, in infants - - - - -	502
Rest pain - - - - -	447
Retina, detachment of, etiology of - - - - -	188
—, —, —, loss of vision in - - - - -	174, 190, 212
—, —, —, symptoms and treatment of - - - - -	191
—, wounds of - - - - -	208
Retinitis, albuminuric - - - - -	179
REVIEWS OF BOOKS:	
Anæsthesia for the poor risk (<i>Mushin</i>) - - - - -	170
—, <i>Modern practice in</i> (<i>Edited by Evans</i>) - - - - -	477
Anæsthetics for medical students (<i>Ostlere</i>) - - - - -	255
Analgesia and anæsthesia, <i>Obstetric</i> (<i>Snyder</i>) - - - - -	170
Anatomy, <i>Gray's</i> (<i>Edited by Johnston and Willis</i>) - - - - -	479
Aviation medicine, its theory and application (<i>Bergin</i>) - - - - -	477
B.C.G. vaccination in theory and practice (<i>Irvine</i>) - - - - -	390
Blood transfusion (<i>De Gowing, Hardin and Alsever</i>) - - - - -	254
— (<i>Edited by Keynes</i>) - - - - -	254
Childbirth, <i>Training for</i> (<i>Randell</i>) - - - - -	567
Chiropody, <i>Essentials of</i> (<i>Pratt</i>) - - - - -	567
—, <i>Principles of</i> (<i>Hanby and Walker</i>) - - - - -	478
Climates, warm, <i>Diseases of</i> (<i>Dubois and van den Berghe</i>) - - - - -	391
Clinical methods (<i>Hutchison and Hunter</i>) - - - - -	171
Cystography and urography (<i>Macalpine</i>) - - - - -	87
Diagnosis, <i>Bedside</i> (<i>Seward</i>) - - - - -	478
—, <i>Symptoms in</i> (<i>Meakins</i>) - - - - -	479
Food biochemistry, <i>Elements of</i> (<i>Peterson, Skinner and Strong</i>) - - - - -	479
— inspection notes (<i>Hill and Dodsworth</i>) - - - - -	479
Forebrain, <i>Evolution of</i> (<i>Schepers</i>) - - - - -	87
Fractures and dislocations in general practice (<i>Hosford</i>) - - - - -	391
Gowers, Sir William (<i>Critchley</i>) - - - - -	254
Hæmatology (<i>Fowler</i>) - - - - -	479
Hæmolytic disease of newborn (<i>Pickles</i>) - - - - -	566
Head, <i>Acute injuries of</i> (<i>Roubootham</i>) - - - - -	567
Heart, <i>Clinical auscultation of</i> (<i>Levine and Harvey</i>) - - - - -	478
Infant feeding, <i>Notes on</i> (<i>Fleming</i>) - - - - -	255
Infants and children, <i>Diagnostic tests for</i> (<i>Behrendt</i>) - - - - -	254
Johns Hopkins, <i>Story of the</i> (<i>Bernheim</i>) - - - - -	566
Kinderpsychiatrie, <i>Lehrbuch der allgemeinen</i> (<i>Tramer</i>) - - - - -	479
Manipulation, joint, <i>Science and art of</i> , Vol. 1, the extremities (<i>Mennell</i>) - - - - -	391
Marriage counselling (<i>Mace</i>) - - - - -	86
Massage and medical gymnastics, <i>Theory and practice of</i> (<i>Goodall-Copestake</i>) - - - - -	255
Maternity in Great Britain (<i>Royal College of Obstetricians and Population Investigation Committee</i>) - - - - -	170
Medicine, Geriatric (<i>Steglitz</i>) - - - - -	479

	PAGE
Paul-Bunnell test for glandular fever	36
Pelvic cancer, sympathetic block in	326
Penicillin, concentration of, in human milk	84
—, in acute osteomyelitis	abs 310
— respiratory infections in infants	502, 504, 505, 506, 507, 508
— boils	163
— chronic pulmonary infections	515
— congenital syphilis	282
— influenza	487
— ophthalmology	194
— pneumonia, mode of administration	515
— respiratory infections, use and abuse of	510
— rheumatism in childhood	285
— skin diseases	298
— streptococcal infections	350
— syphilis	259
— whooping-cough	508
—, insoluble compounds of	259
Periarteritis nodosa, etiology of	399, 402
Perineum, laceration of, during labour, causes of	136
—, —, repair of	139
Peripheral vascular disease, pain in	445
—, —, sympathetic block in	325, 452
Peritonitis, treatment of, comparison of newer antibiotics in	abs 251
Phenolsulphonphthalein excretion test	47
Phlebotomy, postoperative	266, 267
Pholedrine, action of	73
Photometer, M.R.C. grey wedge, for hæmoglobin estimation	RC 77
Physeptone	324
Pink disease, treatment of, B.A.L.	289
Pituitary-adrenal cortical system, anterior, epinephrine stimulation of	369
—, —, hypothalamic, stimulation of by stress	370
— adrenocorticotrophic hormone (ACTH)	368
Placenta prævia, treatment of	276
Plasma as foodstuff	239
— proteins, normal and in impaired kidney function	48
— substitutes, use of	240, 264
Pleural fluids, examination of	23
Pneumoconiosis, etiology of	360
Pneumonia, in infants, treatment of	505, 506, 512
—, primary atypical, clinical features, diagnosis and treatment	498, 499, 500
—, treatment of	350
—, —, oral penicillin	abs 388
—, —, oxygen	520
Pneumothorax in infants, etiology and treatment of	507
Poliomyelitis, etiology and treatment of	350
Polycythæmia vera, treatment of, P ³²	294
Posture, effect of high heels on	221
Practitioner, The, fifty years ago	Advt. p. lvii, liii, lxi, lxxv, lxxvii
Pregnancy and thyrotoxicosis	407
—, eye examination in	175, 180, 181
— in diabetes	277
—, normal, conduct of	275
—, pruritus in	109
—, toxæmias of, treatment of, rutin	abs 85
—, toxæmic albuminuria in	NQ 82
Procaine, intravenous, in postoperative pain	326
— penicillin G in meningitis	287
Progesterone, formula of	420
— implantation therapy, indications for	443
Promizole in tuberculosis	334
Prostate, carcinoma of, diagnosis of, biopsy	317
—, —, treatment of, hormones	316, 343
—, enlargement of, simple, surgery of	314
Prostatectomy, methods of	315
—, nocturnal frequency after	NQ 471
Protein hydrolysates	236, 238, 358
Proteins and amino-acids	357
Prothrombin, formation and action of	549

	PAGE
Squint, treatment of, operative	205
Sterility in male, treatment of, gonadotrophins	435
Sternal puncture	5, 6
Stilbæstrol, formula of	425
Stomach, carcinoma of, treatment of	270, 338
Stools, examination of	13
Streptomycin and <i>para</i> -aminosalicylic acid, relation between	403
— in gastro-enteritis in infants	287
— in meningitis due to <i>H. influenzae</i>	287
— in miliary tuberculosis	285
— in non-tuberculous infections	261
— in peritonitis	abs 563
— in skin tuberculosis	299
— in staphylococcal pneumonia in infants	505
— in tuberculosis	24, 260, 314, 330, 333
— in tuberculous cervical adenitis	286
— in tuberculous meningitis	53, 285
— in urology	313
— in whooping-cough	abs 474, 508
—, toxic effects of, in labyrinthine disease	264
Stress, effects of	393
Sugar tolerance test, technique of	28
Sulphadiazine in meningitis due to <i>H. influenzae</i>	287
Sulphamethazine in urinary infections	abs 474
Sulphathiazole, vaginal instillation of, after delivery	abs 168
Sulphetone in tuberculosis	334
Sulphonamides in acute respiratory infections in infants	502-508
— in influenza	487
— in rheumatism, in childhood	284
— in urology	313
— in whooping-cough	508
Surgery, advances in	266
Sycosis barbae, treatment of	300
Sympathectomy, chemical	NQ 559
Sympathin E	73
Sympathomimetic action and its antagonism	70
Syphilis, congenital, treatment of	282
— in pregnancy, treatment of, penicillin G	abs 252
—, treatment of	259
Testicles, tumours of, urinary gonadotrophins in	432
—, undescended, treatment of, gonadotrophins	434
Testosterone, formula of	421
— implantation therapy, indications for	441
Tetanus immunization	348
Thermal comfort	141, 143, 149
Throat swabs, method of using, and interpretation of report	17, 18, 19
Thrombin, use as hæmostatic	550
Thrombokinasé, action of	550
Thromboplastin, action of	550
Thrombosis, cerebral, in morbus cereuleus, treatment of, oxygen in	522
Thyroid, neoplasms of	411
Thyrototoxicosis, etiology and endemicity of	406, 407
Thyroxine, inhibition of	410
Tinea capitis, etiology of	31
—, treatment of, ointment for	abs 564
—, —, —, phenylmercuric nitrate	299
— corporis, etiology of	32
— cruris, etiology of	31
— pedis, etiology of	31
— unguium, etiology of	33
—, treatment of, thorium-X	NQ 82
Tobacco intoxication, chronic	abs 562
Toes, deformities of, due to high heels	225
Tonsillitis, acute, treatment of	510
— in infants, treatment of	503
Toothache, relief of	abs 476
Trihexypbenidyl ("artane") in Parkinsonism	abs 473
Tubercle bacilli, human and bovine, typing of	24
Tuberculosis immunization	347

	PAGE
Squint, treatment of, operative	205
Sterility in male, treatment of, gonadotrophins	435
Sternal puncture	5, 6
Stilbæstrol, formula of	425
Stomach, carcinoma of, treatment of	270, 338
Stools, examination of	13
Streptomycin and <i>para</i> -aminosalicylic acid, relation between	463
— in gastro-enteritis in infants	287
— in meningitis due to <i>H. influenzae</i>	287
— in miliary tuberculosis	285
— in non-tuberculous infections	261
— in peritonitis	abs 563
— in skin tuberculosis	299
— in staphylococcal pneumonia in infants	505
— in tuberculosis	24, 260, 314, 330, 333
— in tuberculous cervical adenitis	286
— in tuberculous meningitis	53, 285
— in urology	313
— in whooping-cough	abs 474, 508
—, toxic effects of, in labyrinthine disease	264
Stress, effects of	393
Sugar tolerance test, technique of	28
Sulphadiazine in meningitis due to <i>H. influenzae</i>	287
Sulphamethazine in urinary infections	abs 474
Sulphathiazole, vaginal instillation of, after delivery	abs 168
Sulphetrone in tuberculosis	334
Sulphonamides in acute respiratory infections in infants	502-508
— in influenza	487
— in rheumatism, in childhood	284
— in urology	313
— in whooping-cough	508
Surgery, advances in	266
Sycosis barbae, treatment of	300
Sympathectomy, chemical	NQ 559
Sympathin E	73
Sympathomimetic action and its antagonism	70
Syphilis, congenital, treatment of	282
— in pregnancy, treatment of, penicillin G	abs 252
—, treatment of	259
Testicles, tumours of, urinary gonadotrophins in	432
—, undescended, treatment of, gonadotrophins	434
Testosterone, formula of	421
— implantation therapy, indications for	444
Tetanus immunization	348
Thermal comfort	141, 143, 149
Throat swabs, method of using, and interpretation of report	17, 18, 19
Thrombin, use as hæmostatic	550
Thrombokinas, action of	550
Thromboplastin, action of	550
Thrombosis, cerebral, in morbus cæruleus, treatment of, oxygen in	522
Thyroid, neoplasms of	411
Thyrotoxicosis, etiology and endemicity of	406, 407
Thyroxine, inhibition of	410
Tinea capitis, etiology of	31
—, treatment of, ointment for	abs 564
—, —, —, phenylmercuric nitrate	299
— corporis, etiology of	32
— cruris, etiology of	31
— pedis, etiology of	31
— unguis, etiology of	33
—, treatment of, thorium-X	NQ 82
Tobacco intoxication, chronic	abs 562
Toes, deformities of, due to high heels	225
Tonsillitis, acute, treatment of	510
— in infants, treatment of	503
Toothache, relief of	abs 476
Trihexyphenidyl ("artane") in Parkinsonism	abs 473
Tubercle bacilli, human and bovine, typing of	24
Tuberculosis immunization	347

Tuberculosis, miliary, acute, treatment of, streptomycin	-	-	-	-	1
—, pulmonary, bacteriological investigation of	-	-	-	-	
—, —, nursing in	-	-	-	-	NQ
—, —, treatment of, advances in	-	-	-	-	
—, —, —, para-aminosalicylic acid	-	-	-	-	334
—, —, —, streptomycin	-	-	-	-	
—, —, —, sulphones	-	-	-	-	
Typhoid fever, blood cultures in	-	-	-	-	
—, carriers, agglutination test for	-	-	-	-	
—, immunization	-	-	-	-	
—, treatment of, chloromycetin	-	-	-	-	348, abs
Typhus fever, agglutination reactions and tests in	-	-	-	-	38
Tyrosine in skin diseases	-	-	-	-	
Ulceration, pain in	-	-	-	-	
Ulcers, peptic, treatment of, surgical	-	-	-	-	
Ultra-violet light treatment of scalp conditions	-	-	-	-	
Undecylenic acid in fungous infections and psoriasis	-	-	-	-	
Undulant fever, agglutination tests and blood cultures in	-	-	-	-	34
Urea clearance test of Van Slyke, technique of	-	-	-	-	
— concentration test of Maclean and de Wesselow, technique of	-	-	-	-	
Ureters, transplantation of, into bowel	-	-	-	-	
Urethane in cancer	-	-	-	-	
— in leukaemia	-	-	-	-	
Urinary infections, treatment of, sulphamethazine	-	-	-	-	abs
Urine, retention of, acute	-	-	-	-	RC
Urology, advances in	-	-	-	-	
Uterus, bleeding from, prolonged and excessive, treatment of, gonadotrophin	-	-	-	-	
—, cancer of,	-	-	-	-	89, 93, 94, RC
—, curettage and dilatation of	-	-	-	-	118, 119, 1
—, prolapse of	-	-	-	-	111, 1
Uvea, inflammation of, etiology of	-	-	-	-	
Vagina, discharge from, in etiology of pruritus vulvae	-	-	-	-	
—, regressive changes at menopause	-	-	-	-	1
Vaginal smear method in diagnosis of cancer	-	-	-	-	
Vaginitis, senile, at menopause, treatment of	-	-	-	-	1
Vagotomy for peptic ulcer	-	-	-	-	2
Varicose ulcers, treatment of	-	-	-	-	RC, 4
Vascular disease, peripheral, treatment of, glycine	-	-	-	-	abs
Vasomotor crises, sympathetic block in	-	-	-	-	
— disturbance, winter resort for	-	-	-	-	3
Vein, central retinal, obstruction of, results of	-	-	-	-	NQ
Venoms, snake, haemostatic value of	-	-	-	-	174, 2
Vi-agglutination in enteric diseases	-	-	-	-	5
Vineent's infection, treatment of	-	-	-	-	
Vioform, use of, in skin diseases	-	-	-	-	5
Vision, binocular, obstacles to	-	-	-	-	3
—, sudden and rapid failure of, significance and causes of	-	-	-	-	2
Vitamin A, human requirements of	-	-	-	-	173, 2
Vitamin B ₁₂ therapy	-	-	-	-	abs, 4
— supplements, indications for	-	-	-	-	263, 2
Vitamins, advances in	-	-	-	-	3
—, administration of, to members of police force	-	-	-	-	3
Vitreous, haemorrhage into	-	-	-	-	NQ, 2
Volhard's red hypertension	-	-	-	-	1
Vulva, diseases of, local	-	-	-	-	1
Wassermann reaction	-	-	-	-	10
Weil-Felix reaction	-	-	-	-	1
Weil's disease, agglutination reaction in	-	-	-	-	40, 1
Whooping-cough immunization	-	-	-	-	
—, treatment of	-	-	-	-	21
—, —, —, streptomycin	-	-	-	-	
—, —, —, sulphonamides	-	-	-	-	351, 50
Wintrobe's oxalate mixture, preparation of	-	-	-	-	474, 50
World Medical Association, assembly of	-	-	-	-	50
Xiphosternal crunch	-	-	-	-	
X-ray therapy, skin protection with antihistamine ointments in	-	-	-	-	45
Xylocaïne, local anaesthetic	-	-	-	-	47

	PAGE
Tuberculosis, miliary, acute, treatment of, streptomycin	331
—, pulmonary, bacteriological investigation of	20
—, —, nursing in	NQ 472
—, —, treatment of, advances in	328
—, —, —, —, para-aminosalicylic acid	334, 460
—, —, —, —, streptomycin	332
—, —, —, —, sulphones	334
Typhoid fever, blood cultures in	34
—, carriers, agglutination test for	39
—, immunization	348
—, treatment of, chloromycetin	348, abs 561
Typhus fever, agglutination reactions and tests in	38, 40
Tyrosine in skin diseases	298
Ulceration, pain in	419
Ulcers, peptic, treatment of, surgical	267
Ultra-violet light treatment of scalp conditions	220
Undecylenic acid in fungous infections and psoriasis	299
Undulant fever, agglutination tests and blood cultures in	34, 39
Urea clearance test of Van Slyke, technique of	45
— concentration test of Maclean and de Wesselow, technique of	44
Ureters, transplantation of, into bowel	318
Urethane in cancer	342
— in leukaemia	296
Urinary infections, treatment of, sulphamethazine	abs 474
Urine, retention of, acute	RC 383
Urology, advances in	313
Uterus, bleeding from, prolonged and excessive, treatment of, gonadotrophin	435
—, cancer of,	89, 93, 94, RC 555
—, curettage and dilatation of	118, 119, 211
—, prolapse of	111, 116
Uvea, inflammation of, etiology of	177
Vagina, discharge from, in etiology of pruritus vulvae	106
—, regressive changes at menopause	104
Vaginal smear method in diagnosis of cancer	90
Vaginitis, senile, at menopause, treatment of	104
Vagotomy for peptic ulcer	268
Varicose ulcers, treatment of	RC 467
Vascular disease, peripheral, treatment of, glycine	abs 84
Vasomotor crises, sympathetic block in	325
— disturbance, winter resort for	NQ 81
Vein, central retinal, obstruction of, results of	174, 212
Venoms, snake, haemostatic value of	553
Vi-agglutination in enteric diseases	39
Vincent's infection, treatment of	511
Vioform, use of, in skin diseases	300
Vision, binocular, obstacles to	204
—, sudden and rapid failure of, significance and causes of	173, 212
Vitamin A, human requirements of	abs 475
Vitamin B ₁₂ therapy	263, 292
— supplements, indications for	354
Vitamins, advances in	358
—, administration of, to members of police force	NQ 249
Vitreous, haemorrhage into	174
Volhard's red hypertension	180
Vulva, diseases of, local	107
Wassermann reaction	52
Weil-Felix reaction	40, 41
Weil's disease, agglutination reaction in	42
Whooping-cough immunization	283
—, treatment of	351, abs 351, 507
—, —, —, streptomycin	474, 508
—, —, —, sulphonamides	508
Wintrobe's oxalate mixture, preparation of	3
World Medical Association, assembly of	458
Xiphosternal crunch	abs 476
X-ray therapy, skin protection with antihistamine ointments in	abs 469
Xylocaine, local anæsthetic	244

